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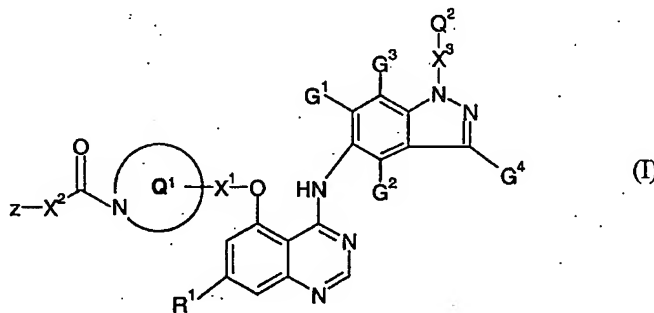
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(54) Title: INDAZOLYLAMINO QIONAZOLINE DERIVATIVES AS ANTITUMOR AGENTS



(57) Abstract: A quinazoline derivative of the Formula (I): wherein the substituents are as defined in the text for use in the production of an anti-proliferative effect which effect is produced alone or in part by inhibiting erbB2 receptor tyrosine kinase in a warm-blooded animal such as man.

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## INDAZOLYLAMINO QUINAZOLINE DERIVATIVES AS ANTITUMOR AGENTS

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are  
5 accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

- 10 Many of the current treatment regimes for diseases resulting from the abnormal regulation of cellular proliferation such as psoriasis and cancer, utilise compounds that inhibit DNA synthesis and cellular proliferation. To date, compounds used in such treatments are generally toxic to cells however their enhanced effects on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to these cytotoxic anti-tumour agents  
15 are currently being developed, for example selective inhibitors of cell signalling pathways. These types of inhibitors are likely to have the potential to display an enhanced selectivity of action against tumour cells and so are likely to reduce the probability of the therapy possessing unwanted side effects.

Eukaryotic cells are continually responding to many diverse extracellular signals that  
20 enable communication between cells within an organism. These signals regulate a wide variety of physical responses in the cell including proliferation, differentiation, apoptosis and motility. The extracellular signals take the form of a diverse variety of soluble factors including growth factors and other autocrine, paracrine and endocrine factors. By binding to specific transmembrane receptors, these ligands integrate the extracellular signal to the  
25 intracellular signalling pathways, therefore transducing the signal across the plasma membrane and allowing the individual cell to respond to its extracellular signals. Many of these signal transduction processes utilise the reversible process of the phosphorylation of proteins that are involved in the promotion of these diverse cellular responses. The phosphorylation status of target proteins is regulated by specific kinases and phosphatases that  
30 are responsible for the regulation of about one third of all proteins encoded by the mammalian genome. As phosphorylation is such an important regulatory mechanism in the signal

transduction process, it is therefore not surprising that aberrations in these intracellular pathways result in abnormal cell growth and differentiation and so promote cellular transformation (reviewed in Cohen *et al*, Curr Opin Chem Biol, 1999, 3, 459-465).

It has been widely shown that a number of these tyrosine kinases are mutated to  
5 constitutively active forms and/or when over-expressed result in the transformation of a variety of human cells. These mutated and over-expressed forms of the kinase are present in a large proportion of human tumours (reviewed in Kolibaba *et al*, Biochimica et Biophysica Acta, 1997, 133, F217-F248). As tyrosine kinases play fundamental roles in the proliferation and differentiation of a variety of tissues, much focus has centred on these enzymes in the  
10 development of novel anti-cancer therapies. This family of enzymes is divided into two groups - receptor and non-receptor tyrosine kinases e.g. EGF Receptors and the SRC family respectively. From the results of a large number of studies including the Human Genome Project, about 90 tyrosine kinase have been identified in the human genome, of this 58 are of the receptor type and 32 are of the non-receptor type. These can be compartmentalised into  
15 20 receptor tyrosine kinase and 10 non-receptor tyrosine kinase sub-families (Robinson *et al*, Oncogene, 2000, 19, 5548-5557).

The receptor tyrosine kinases are of particular importance in the transmission of mitogenic signals that initiate cellular replication. These large glycoproteins, which span the plasma membrane of the cell possess an extracellular binding domain for their specific ligands  
20 (such as Epidermal Growth Factor (EGF) for the EGF Receptor). Binding of ligand results in the activation of the receptor's kinase enzymatic activity that resides in the intracellular portion of the receptor. This activity phosphorylates key tyrosine amino acids in target proteins, resulting in the transduction of proliferative signals across the plasma membrane of the cell.

25 It is known that the erbB family of receptor tyrosine kinases, which include EGFR, erbB2, erbB3 and erbB4, are frequently involved in driving the proliferation and survival of tumour cells (reviewed in Olayioye *et al*, EMBO J, 2000, 19, 3159). One mechanism in which this can be accomplished is by overexpression of the receptor at the protein level, generally as a result of gene amplification. This has been observed in many common human  
30 cancers (reviewed in Klapper *et al*, Adv. Cancer Res., 2000, 77, 25) such as breast cancer (Sainsbury *et al*, Brit. J. Cancer, 1988, 58, 458; Guerin *et al*, Oncogene Res., 1988, 3, 21;

Slamon *et al.*, *Science*, 1989, 244, 707; Klijn *et al.*, *Breast Cancer Res. Treat.*, 1994, 29, 73 and reviewed in Salomon *et al.*, *Crit. Rev. Oncol. Hematol.*, 1995, 19, 183), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny *et al.*, *Brit. J. Cancer*, 1986, 54, 265; Reubi *et al.*, *Int. J. Cancer*, 1990, 45, 269; Rusch *et al.*, *Cancer Research*, 1993, 53, 2379; 5 Brabender *et al.*, *Clin. Cancer Res.*, 2001, 7, 1850) as well as other cancers of the lung (Hendler *et al.*, *Cancer Cells*, 1989, 7, 347; Ohsaki *et al.*, *Oncol. Rep.*, 2000, 7, 603), bladder cancer (Neal *et al.*, *Lancet*, 1985, 366; Chow *et al.*, *Clin. Cancer Res.*, 2001, 7, 1957, Zhau *et al.*, *Mol. Carcinog.*, 3, 254), oesophageal cancer (Mukaida *et al.*, *Cancer*, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen *et al.*, *Oncogene Res.*, 10 1987, 1, 149; Kapitanovic *et al.*, *Gastroenterology*, 2000, 112, 1103; Ross *et al.*, *Cancer Invest.*, 2001, 19, 554), cancer of the prostate (Visakorpi *et al.*, *Histochem. J.*, 1992, 24, 481; Kumar *et al.*, 2000, 32, 73; Scher *et al.*, *J. Natl. Cancer Inst.*, 2000, 92, 1866), leukaemia (Konaka *et al.*, *Cell*, 1984, 37, 1035, Martin-Subero *et al.*, *Cancer Genet Cytogenet.*, 2001, 127, 174), ovarian (Hellstrom *et al.*, *Cancer Res.*, 2001, 61, 2420), head and neck (Shiga *et al.*, *Head Neck*, 2000, 22, 599) or pancreatic cancer (Ovotny *et al.*, *Neoplasma*, 2001, 48, 188). As more human tumour tissues are tested for expression of the erbB family of receptor tyrosine kinases it is expected that their widespread prevalence and importance will be further enhanced in the future.

As a consequence of the mis-regulation of one or more of these receptors (in particular 20 erbB2), it is widely believed that many tumours become clinically more aggressive and so correlate with a poorer prognosis for the patient (Brabender *et al.*, *Clin. Cancer Res.*, 2001, 7, 1850; Ross *et al.*, *Cancer Investigation*, 2001, 19, 554, Yu *et al.*, *Bioessays*, 2000, 22, 673).

In addition to these clinical findings, a wealth of pre-clinical information suggests that the erbB family of receptor tyrosine kinases are involved in cellular transformation. This 25 includes the observations that many tumour cell lines overexpress one or more of the erbB receptors and that EGFR or erbB2 when transfected into non-tumour cells have the ability to transform these cells. This tumourigenic potential has been further verified as transgenic mice that overexpress erbB2 spontaneously develop tumours in the mammary gland. In addition to this, a number of pre-clinical studies have demonstrated that anti-proliferative 30 effects can be induced by knocking out one or more erbB activities by small molecule inhibitors, dominant negatives or inhibitory antibodies (reviewed in Mendelsohn *et al.*, *Oncogene*, 2000, 19, 6550). Thus it has been recognised that inhibitors of these receptor



tyrosine kinases should be of value as a selective inhibitor of the proliferation of mammalian cancer cells (Yaish *et al.* Science, 1988, 242, 933, Kolibaba *et al.*, *Biochimica et Biophysica Acta*, 1997, 133, F217-F248; Al-Obeidi *et al.*, 2000, Oncogene, 19, 5690-5701; Mendelsohn *et al.*, 2000, Oncogene, 19, 6550-6565).

5 In addition to this pre-clinical data, the small molecule EGFR tyrosine kinase inhibitors Iressa® (also known as gefitinib and ZD1839) and Tarceva® (also known as erlotinib and CP-358,774) have been approved for use in the treatment of advanced non-small cell lung cancer. Furthermore, inhibitory antibodies against EGFR and erbB2 (erbitux® (c-225 / cetuximab) and herceptin® (trastuzumab) respectively) have proven to be beneficial  
10 in the clinic for the treatment of selected solid tumours (reviewed in Mendelsohn *et al.*, 2000, Oncogene, 19, 6550-6565).

Recently mutations in the ATP binding pocket of the intracellular catalytic domain of the EGF receptor have been discovered in certain sub-sets of non-small cell lung cancers (NSCLCs). The presence of mutations in the receptor appear to correlate with response to  
15 EGFR tyrosine kinase inhibitors such as gefitinib (Lynch *et al.*, *N Engl J Med* 2004; 350: 2129-2139; Paez *et al.*, *Science* 2004; 304: 1497-1500), although it is becoming evident that the clinical benefits of compounds such as gefitinib and erlotinib are not likely to be mediated by EGFR mutations alone. It has been demonstrated that ligand stimulation results in a different phosphorylation pattern in mutated receptors compared with that seen in wild-type  
20 receptors and it is thought that mutant EGF receptors selectively transduce survival signals on which NSCLCs become dependent. Inhibition of those signals by compounds such as gefitinib may contribute to the efficacy of such drugs (Sordella *et al.*, *Science* 2004; 305: 1163-1167). Similarly, mutations within the erbB2 kinase domain have recently been discovered in certain primary tumours, such as NSCLC, glioblastoma and gastric and ovarian  
25 tumours (Stephens *et al.*, *Nature* 2004; 431; 525-526). Accordingly the inhibition of the EGF and/or erbB2 tyrosine kinase in both wild-type and mutated receptors is an important target that would be expected to provide an anti-cancer effect.

Amplification and/or activity of members of the erbB type receptor tyrosine kinases have been detected and so have been implicated to play a role in a number of non-malignant  
30 proliferative disorders such as psoriasis (Ben-Bassat, Curr. Pharm. Des., 2000, 6, 933; Elder *et al.*, *Science*, 1989, 243, 811), benign prostatic hyperplasia (BPH) (Kumar *et al.*, Int. Urol.

Nephrol., 2000, 32,73), atherosclerosis and restenosis (Bokemeyer et al., Kidney Int., 2000, 58, 549). It is therefore expected that inhibitors of erbB type receptor tyrosine kinases will be useful in the treatment of these and other non-malignant disorders of excessive cellular proliferation.

5 WO 96/09294, WO 96/15118, WO 96/16960, WO 96/30347, WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980, WO 96/33981, WO 97/03069, WO 97/13771, WO 97/30034, WO 97/30035, WO 97/38983, WO 98/02437, WO 98/02434, WO 98/02438, WO 98/13354, WO 99/35132, WO 99/35146, WO 01/21596, WO 01/55141 and WO 02/18372 each disclose that certain quinazoline derivatives which bear an anilino substituent at the  
10 4-position possess receptor tyrosine kinase inhibitory activity.

WO 01/94341 discloses that certain quinazoline derivatives which carry a 5-substituent are inhibitors of the Src family of non-receptor tyrosine kinases, such as c-Src, c-Yes and c-Fyn.

WO 03/040108 and WO 03/040109 each disclose that certain quinazoline derivatives  
15 which carry a 5-substituent are inhibitors of the erbB family of receptor tyrosine kinases, particularly EGF and erbB2 receptor tyrosine kinases. WO 03/040108 and WO 03/040109 each disclose certain 4-(indazol-5-ylamino)quinazoline compounds that contain a 1-methylpiperidin-4-yloxy group at the 5-position on the quinazoline ring. In these compounds, the piperidin-4-yloxy group is substituted at the 1-position (i.e. at the ring nitrogen atom) by a  
20 methyl group only. There is no alkanoyl substituent at the 1-position on the piperidin-4-yloxy group (i.e. at the ring nitrogen atom).

WO 03/082831 and WO 2005/012290 each disclose certain 4-anilino quinazoline compounds that contain a substituent at the 6-position on the quinazoline ring and their use as inhibitors of the erbB family of receptor tyrosine kinases (particularly of EGF receptor  
25 tyrosine kinase). There is no disclosure in WO 03/082831 and WO 2005/012290 of a quinazoline compound that carries an indazol-5-ylamino group at the 4-position on the quinazoline ring or a substituent at the 5-position on the quinazoline ring.

WO 2005/030757 discloses certain 4-substituted quinazoline compounds that contain a substituent at the 6- and/or 7-position on the quinazoline ring and their use as inhibitors of  
30 the erbB family of receptor tyrosine kinases (particularly of EGF receptor tyrosine kinase).

There is no disclosure in WO 2005/030757 of a quinazoline compound that carries an indazol-5-ylamino group at the 4-position on the quinazoline ring or an alkanoyl containing substituent at the 5-position on the quinazoline ring.

WO 2004/096226 discloses that certain quinazoline derivatives that are substituted at  
5 the 5-position with a substituent containing certain substituted pyrrolidinyl groups possess potent anti-tumour activity, for example by way of inhibition of EGF and/or erbB2 receptor tyrosine kinases, especially EGF receptor tyrosine kinase. The quinazoline derivatives disclosed in WO 2004/096226 carry a substituted anilino substituent at the 4-position on the quinazoline ring. There is no disclosure in WO 2004/096226 of a quinazoline compound that  
10 carries an indazol-5-ylamino group at the 4-position on the quinazoline ring.

WO 2005/026152 discloses that certain quinazoline derivatives that are substituted at the 5-position with a substituent containing certain substituted alkanoyl groups possess potent anti-tumour activity, for example by way of inhibition of EGF and/or erbB2 receptor tyrosine kinases. The quinazoline derivatives disclosed in WO 2005/026152 carry a substituted  
15 anilino substituent at the 4-position on the quinazoline ring. There is no disclosure in WO 2005/026152 of a quinazoline compound that carries an indazol-5-ylamino group at the 4-position on the quinazoline ring.

However, there remains a need to find further compounds with good *in-vivo* activity together with improved pharmacological characteristics compared with known erbB tyrosine  
20 kinase inhibitors, particularly compounds that are selective erbB2 tyrosine kinase inhibitors. For example, there is a need for novel compounds with advantageous and/or improved characteristics in, but not limited to, for example, (i) physical properties; (ii) favourable DMPK properties, such as high bioavailability and/ or advantageous half life and/or advantageous volume of distribution and/or high absorption; (iii) factors that decrease the  
25 liability for clinical drug-drug interactions (e.g. cytochrome P450 enzyme inhibition or induction); and (iv) compounds with a reduced liability for QT interval prolongation in patients, for example compounds which are inactive or weakly active in a HERG assay.

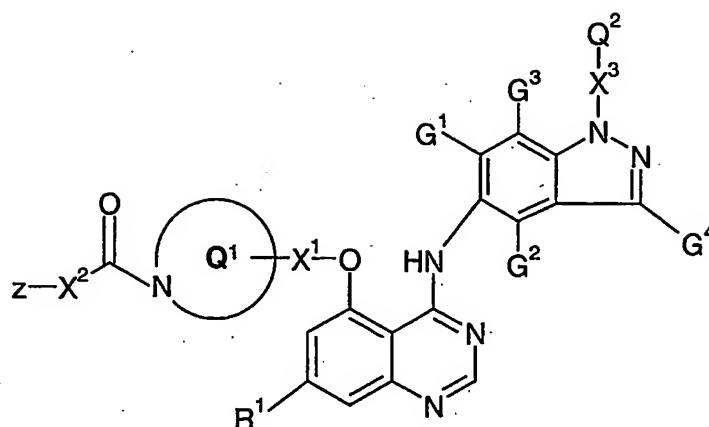
Surprisingly, we have now found that a select group of 4-(indazol-5-ylamino)quinazoline compounds substituted at the 5-position with a substituent containing  
30 certain alkanoyl groups possess potent anti-tumour activity. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by

virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the erbB family of receptor tyrosine kinases that are involved in the signal transduction steps which lead to the proliferation of tumour cells. In particular, it is believed that the compounds of the present invention provide  
5 an anti-tumour effect by way of inhibition of EGF and/or erbB2 receptor tyrosine kinases. More particularly, it is believed that the compounds of the present invention provide an anti-tumour effect by way of the selective inhibition of erbB2 receptor tyrosine kinase, compared to EGF receptor tyrosine kinase. It is also believed that the compounds of the present invention exhibit a combination of favourable properties, such as those described  
10 hereinbefore. For example, generally the compounds according to the invention exhibit favourable DMPK properties, for example high free-plasma levels.

References to erbB receptors, particularly erbB2, used herein are intended to include both wild-type and mutated receptors unless specifically stated otherwise. The term "mutation" includes, but is not limited to, gene amplification, nucleotide in-frame deletions or  
15 substitutions in one or more of the exons that encode receptors such as erbB2.

Generally the compounds of the present invention possess potent inhibitory activity against the erbB receptor tyrosine kinase family, for example by inhibition of EGF and/or erbB2 and/or erbB4 receptor tyrosine kinases, whilst possessing less potent inhibitory activity against other kinases. Furthermore, generally the compounds of the present invention possess  
20 substantially better potency against the erbB2 tyrosine kinase over that of the EGFR tyrosine kinase, thus potentially providing effective treatment for erbB2 driven tumours. Accordingly, it may be possible to administer a compound according to the present invention at a dose that is sufficient to inhibit erbB2 tyrosine kinase whilst having no significant effect upon EGFR or other tyrosine kinases. The selective inhibition provided by the compounds according to the  
25 present invention may provide treatments for conditions mediated by erbB2 tyrosine kinase, whilst reducing undesirable side effects that may be associated with the inhibition of other tyrosine kinases.

According to a first aspect of the invention there is provided a quinazoline derivative of the Formula I:



I

wherein:

$R^1$  is selected from hydrogen, hydroxy, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkoxy;

$X^1$  is selected from a direct bond and  $C(R^2)_2$ , wherein each  $R^2$ , which may be the same  
5 or different, is selected from hydrogen and (1-4C)alkyl;

ring  $Q^1$  is a 4, 5, 6 or 7 membered saturated or partially unsaturated heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 or 2 additional heteroatoms independently selected from oxygen, nitrogen and sulfur, and which ring is linked to the group  $X^1$  by a ring carbon atom;

10  $X^2$  is a group of the formula  $-(CR^3R^4)_p-$ , wherein (i)  $p$  is 1, 2, 3 or 4 and each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-4C)alkyl, or (ii)  $p$  is 1 and  $R^3$  and  $R^4$  together with the carbon atom to which they are attached represent a cyclopropyl ring;

$Z$  is selected from hydroxy, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

15  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$ , which may be the same or different, are each selected from hydrogen and halogeno;

$X^3$  is selected from  $SO_2$ ,  $CO$ ,  $SO_2N(R^5)$  and  $C(R^5)_2$ , wherein each  $R^5$ , which may be the same or different, is selected from hydrogen and (1-4C)alkyl; and

Q<sup>2</sup> is aryl or heteroaryl, which aryl or heteroaryl group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, cyano and (1-6C)alkoxy;

and any heterocyclyl group represented by Q<sup>1</sup> optionally bears 1 or 2 oxo or thioxo  
5 substituents;

or a pharmaceutically-acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only,  
10 references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy and ethoxy, (1-6C)alkylamino includes methylamino and ethylamino, and di-[(1-6Calkyl)amino] includes dimethylamino and diethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined  
15 above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. In particular, the quinazoline derivative of the Formula I has a chiral centre on the ring Q<sup>1</sup> at the ring carbon atom attached to the group X<sup>1</sup>. The present invention encompasses all such stereoisomers having activity as herein  
20 defined, for example the (2R) and (2S) isomers (particularly the (2R) isomers). It is further to be understood that in the names of chiral compounds (*R,S*) denotes any scalemic or racemic mixture while (*R*) and (*S*) denote the enantiomers. In the absence of (*R,S*), (*R*) or (*S*) in the name it is to be understood that the name refers to any scalemic or racemic mixture, wherein a scalemic mixture contains *R* and *S* enantiomers in any relative proportions and a racemic  
25 mixture contains *R* and *S* enantiomers in the ratio 50:50. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

30 Suitable values for the generic radicals referred to above include those set out below.

A suitable value for  $Q^2$  when it is aryl is, for example, phenyl or naphthyl, preferably phenyl.

A suitable value for  $Q^2$  when it is heteroaryl is, for example, an aromatic 5 or 6 membered monocyclic ring with up to 4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl. A particular value for  $Q^2$  when it is heteroaryl is, for example, an aromatic 5 or 6 membered monocyclic ring containing nitrogen and, optionally, 1 or 2 (for example 1) additional ring heteroatoms independently selected from oxygen, nitrogen and sulfur, for example pyrrolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl.

A suitable value for the ring  $Q^1$  (also referred to herein simply as " $Q^1$ ") is, for example, a non-aromatic saturated (i.e. ring systems with the maximum degree of saturation) or partially unsaturated (i.e. ring systems retaining some, but not the full, degree of unsaturation) 4, 5, 6 or 7 membered monocyclic heterocyclyl group with up to 5 heteroatoms independently selected from oxygen, nitrogen and sulfur, provided at least one heteroatom is nitrogen and which ring is linked to the group  $X^1$  by a ring carbon atom. Suitable values include, for example, azetidyl, pyrrolinyl, pyrrolidinyl, morpholinyl (including morpholino), tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl (including piperidino), homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl. A nitrogen or sulfur atom within a heterocyclyl group may be oxidized to give the corresponding N or S oxide. A suitable value for a heterocyclyl group that bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

Another suitable value for  $Q^1$  is a 4, 5, 6 or 7 membered monocyclic heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 or 2 further heteroatoms independently selected from oxygen, nitrogen and sulfur, which heterocyclyl group may be fully saturated or partially unsaturated and is linked to the group  $X^1$  by a ring carbon atom. More particularly  $Q^1$  is a 5 or 6 membered monocyclic heterocyclyl group containing 1

- nitrogen heteroatom and optionally 1 further heteroatom selected from oxygen, nitrogen and sulfur, which heterocyclyl group may be partially unsaturated or preferably fully saturated and is linked to the group  $X^1$  by a ring carbon atom. Still more particularly  $Q^1$  is a monocyclic fully saturated 5 or 6 membered monocyclic heterocyclyl group containing 1 nitrogen
- 5 heteroatom and optionally 1 further heteroatom selected from oxygen, nitrogen and sulfur, which heterocyclyl group is linked to the group  $X^1$  by a ring carbon atom. Even more particularly  $Q^1$  is a monocyclic fully saturated 5 or 6 membered monocyclic heterocyclyl group containing 1 nitrogen heteroatom, which heterocyclyl group is linked to the group  $X^1$  by a ring carbon atom.
- 10 Suitable values of groups represented by  $Q^1$  include azetidiny, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl (all of which are linked to  $X^1$  by a ring carbon atom), more particularly, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-4-yl, piperidin-3-yl, piperidin-2-yl, piperazin-2-yl, piperazin-3-yl, morpholin-2-yl or morpholin-3-yl, and still more particularly pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-2-yl,
- 15 piperazin-2-yl, piperazin-3-yl, morpholin-2-yl or morpholin-3-yl and even more particularly pyrrolidin-2-yl or piperidin-2-yl.

- The mandatory nitrogen heteroatom in the heterocyclyl group  $Q^1$  is attached to the group  $ZX^2C(O)-$ . For the avoidance of any doubt the nitrogen atom in  $Q^1$  to which the group  $ZX^2C(O)-$  is attached is not quaternised; namely the group  $ZX^2C(O)-$  is attached to the
- 20 nitrogen atom in  $Q^1$  via substitution of an NH group in the heterocyclyl ring, for example when  $Q^1$  is pyrrolidin-2-yl the  $ZX^2C(O)-$  group is attached to the pyrrolidin-2-yl ring at the 1-position.

Suitable values for any of the 'R' groups ( $R^1$  to  $R^5$ ), for any of the 'G' groups ( $G^1$  to  $G^4$ ) or for various groups within a  $Q^1$ ,  $Q^2$ ,  $X^1$ ,  $X^2$ ,  $X^3$  or Z group include:-

- |                       |  |
|-----------------------|--|
| 25 for halogeno       | fluoro, chloro, bromo and iodo;                                      |
| for (1-4C)alkyl:      | methyl, ethyl, propyl, isopropyl and <u>tert</u> -butyl;             |
| for (1-6C)alkoxy:     | methoxy, ethoxy, propoxy, isopropoxy and butoxy;                     |
| for (1-6C)alkylamino: | methylamino, ethylamino, propylamino, isopropylamino and butylamino; |



for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino, <u>N</u> -ethyl- <u>N</u> -methylamino and diisopropylamino; and
for (1-4C)alkoxy(1-4C)alkoxy	ethoxymethoxy, propoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy, ethoxypropoxy, methoxyisopropoxy and methoxybutoxy.

5

When, as defined hereinbefore, in the group of the formula  $-X^3-Q^2$ ,  $X^3$  is, for example, a  $SO_2N(R^5)$  linking group, it is the  $SO_2$  group of the  $SO_2N(R^5)$  linking group which is attached to the indazole group in the Formula I and the nitrogen atom which is attached to the  $Q^2$  group.

10 It is to be understood that certain compounds of the Formula I may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which exhibit an inhibitory effect on an erbB receptor tyrosine kinase, such as anti-proliferative activity.

It is also to be understood that certain compounds of the Formula I may exhibit  
15 polymorphism, and that the invention encompasses all such forms which exhibit an inhibitory effect on an erbB receptor tyrosine kinase, such as anti-proliferative activity.

It is also to be understood that the invention relates to all tautomeric forms of the compounds of the Formula I which exhibit an inhibitory effect on an erbB receptor tyrosine kinase, such as anti-proliferative activity.

20 A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid. Suitable inorganic acids include, for example, hydrochloric, hydrobromic or sulfuric acid. Suitable organic acids include, for example, trifluoroacetic, citric or maleic acid. Another suitable pharmaceutically-acceptable salt of a  
25 compound of the Formula I is for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of  $R^1$ ,  $G^1$ ,  $G^2$ ,  $G^3$ ,  $G^4$ ,  $Q^1$ ,  $Q^2$ ,  $X^1$ ,  $X^2$ ,  $X^3$  and  $Z$  has any of the meanings defined hereinbefore or in paragraphs (a) to (mmm) hereinafter :-

- 5 (a)  $R^1$  is selected from hydrogen, hydroxy, methoxy, ethoxy and methoxyethoxy;
- (b)  $R^1$  is selected from hydrogen and methoxy;
- (c)  $R^1$  is hydrogen;
- (d)  $X^1$  is selected from a direct bond and  $C(R^2)_2$ , wherein each  $R^2$ , which may be the same or different, is selected from hydrogen and methyl;
- 10 (e)  $X^1$  is selected from a direct bond,  $CH_2$  and  $CH(CH_3)$ ;
- (f)  $X^1$  is selected from a direct bond and  $CH_2$ ;
- (g)  $X^1$  is  $C(R^2)_2$ , wherein each  $R^2$ , which may be the same or different, is selected from hydrogen and (1-4C)alkyl (particularly (1-2C)alkyl, for example methyl);
- (h)  $X^1$  is  $CH_2$ ;
- 15 (i)  $X^1$  is  $CH(CH_3)$ ;
- (j)  $X^1$  is a direct bond;
- (k)  $Q^1$  is a 5 or 6 membered saturated heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 or 2 (for example 1) additional heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein  $Q^1$  is linked to the group  $X^1$  by a ring
- 20 carbon atom;
- (l)  $Q^1$  is selected from azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl and thiomorpholinyl, wherein  $Q^1$  is linked to the group  $X^1$  by a ring carbon atom;
- (m)  $Q^1$  is selected from pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, wherein  $Q^1$  is linked to the group  $X^1$  by a ring carbon atom;

- (n)  $Q^1$  is selected from azetidiny, pyrrolidinyl, piperidinyl and homopiperidinyl, wherein  $Q^1$  is linked to the group  $X^1$  by a ring carbon atom;
- (o)  $Q^1$  is selected from pyrrolidinyl and piperidinyl, wherein  $Q^1$  is linked to the group  $X^1$  by a ring carbon atom;
- 5 (p)  $Q^1$  is piperidinyl (particularly piperidin-2-yl or piperidin-3-yl, more particularly piperidin-2-yl), wherein  $Q^1$  is linked to the group  $X^1$  by a ring carbon atom;
- (q)  $Q^1$  is pyrrolidinyl (particularly pyrrolidin-2-yl or pyrrolidin-3-yl, more particularly pyrrolidin-2-yl), wherein  $Q^1$  is linked to the group  $X^1$  by a ring carbon atom;
- (r)  $Q^1$  is selected from azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, 10 morpholinyl and thiomorpholinyl (particularly pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, more particularly pyrrolidinyl and piperidinyl), wherein  $Q^1$  is linked to the group  $X^1$  by a ring carbon atom; and

$X^1$  is selected from a direct bond,  $CH_2$  and  $CH(CH_3)$ ;

- (s)  $Q^1$  is selected from pyrrolidinyl and piperidinyl, wherein  $Q^1$  is linked to the group  $X^1$  15 by a ring carbon atom; and

$X^1$  is  $CH_2$ ;

- (t)  $Q^1-X^1$  is selected from pyrrolidin-2-ylmethyl, pyrrolidin-3-ylmethyl, morpholin-2-ylmethyl, morpholin-3-ylmethyl, piperidin-2-ylmethyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl and piperazin-2-ylmethyl;
- 20 (u)  $Q^1-X^1$  is selected from pyrrolidin-2-ylmethyl and piperidin-2-ylmethyl;
- (v)  $Q^1-X^1$  is selected from (2R)-pyrrolidin-2-ylmethyl, (2S)-pyrrolidin-2-ylmethyl, (3R)-pyrrolidin-3-ylmethyl, (3S)-pyrrolidin-3-ylmethyl, (2R)-piperidin-2-ylmethyl, (2S)-piperidin-2-ylmethyl, (3R)-piperidin-3-ylmethyl, (3S)-piperidin-3-ylmethyl, (2R)-piperazin-2-ylmethyl, (2S)-piperazin-2-ylmethyl, (3R)-piperazin-3-ylmethyl, (3S)-piperazin-3-ylmethyl, (2R)-morpholin-2-ylmethyl, (2S)-morpholin-2-ylmethyl, (3R)-morpholin-3-ylmethyl and (3S)-morpholin-3-ylmethyl;
- 25

(w)  $Q^1-X^1$  is selected from (2R)-pyrrolidin-2-ylmethyl and (2S)-pyrrolidin-2-ylmethyl;

(x)  $Q^1-X^1$  is selected from (2R)-piperidin-2-ylmethyl and (2S)-piperidin-2-ylmethyl;

For the avoidance of any doubt, the rings represented by  $Q^1$  described in (k) to (x) above are all substituted on the ring nitrogen by the group  $Z-X^2-C(O)-$  in accordance with  
5 Formula I;

(y)  $X^2$  is a group of the formula  $-(CR^3R^4)_p-$ , wherein (i)  $p$  is 1, 2 or 3 (particularly 1 or 2) and each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl, or (ii)  $p$  is 1 and  $R^3$  and  $R^4$  together with the carbon atom to which they are attached represent a cyclopropyl ring;

10 (z)  $X^2$  is a group of the formula  $-(CR^3R^4)_p-$ , wherein  $p$  is 1, 2 or 3 (particularly 1 or 2) and each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl;

(aa)  $X^2$  is a group of the formula  $-(CR^3R^4)_p-$ , wherein  $p$  is 1 and  $R^3$  and  $R^4$  together with the carbon atom to which they are attached represent a cyclopropyl ring;

15 (bb)  $X^2$  is selected from a group of the formula  $-(CR^3R^4)-$ ,  $-(CR^3R^4CH_2)-$ ,  $-(CR^3R^4CH_2CH_2)-$ ,  $-(CH_2CR^3R^4)-$  and  $-(CH_2CH_2CR^3R^4)-$ , wherein each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl, provided that at least one  $R^3$  or  $R^4$  group in  $X^2$  is (1-2C)alkyl;

(cc)  $X^2$  is selected from a group of the formula  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  
20  $-(CR^3R^4)-$ ,  $-(CR^3R^4CH_2)-$  and  $-(CH_2CR^3R^4)-$ , wherein each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl, provided that  $R^3$  and  $R^4$  are not both hydrogen;

(dd)  $X^2$  is selected from a group of the formula  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-(CHR^3)-$ ,  $-(CHR^3CH_2)-$  and  $-(CH_2CHR^3)-$ , wherein  $R^3$  is selected from hydrogen and (1-2C)alkyl;

25 (ee)  $X^2$  is selected from a group of the formula  $-(CH_2)_p-$ , wherein  $p$  is 1, 2 or 3, (particularly  $p$  is 1 or 2);

(ff)  $X^2$  is a group of the formula  $-(CH_2)_p-$ , wherein  $p$  is 1;

- (gg) Z is selected from hydroxy, amino, methylamino, ethylamino, dimethylamino, N-methyl-N-ethylamino and di-ethylamino;
- (hh) Z is selected from hydroxy and dimethylamino;
- (ii) Z is hydroxy;
- 5 (jj) Z is as defined in any of (gg) to (ii) above and  $X^2$  is selected from a group of the formula  $-\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2-$ ,  $-(\text{CHR}^3)-$ ,  $-(\text{CHR}^3\text{CH}_2)-$  and  $-(\text{CH}_2\text{CHR}^3)-$ , wherein  $R^3$  is selected from hydrogen and (1-2C)alkyl;
- (kk) Z is as defined in any of (gg) to (ii) above and  $X^2$  is a group of the formula  $-(\text{CH}_2)_p-$ , wherein p is 1;
- 10 (ll) Z is as defined in any of (gg) to (ii) above and  $X^2$  is a group of the formula  $-(\text{CR}^3\text{R}^4)_p-$ , wherein p is 1 and  $R^3$  and  $R^4$  together with the carbon atom to which they are attached represent a cyclopropyl ring;
- (mm)  $Z-X^2-$  is hydroxymethyl;
- (nn)  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$ , which may be the same or different, are each selected from  
15 hydrogen, chloro and fluoro;
- (oo)  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  are all hydrogen;
- (pp)  $X^3$  is  $\text{C}(\text{R}^5)_2$  wherein each  $\text{R}^5$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl;
- (qq)  $X^3$  is  $\text{CH}_2$ ;
- 20 (rr)  $Q^2$  is selected from phenyl and a 5 or 6 membered monocyclic heteroaryl ring, which ring contains 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, selected from halogeno, cyano and (1-6C)alkoxy;
- (ss)  $Q^2$  is selected from phenyl and a 5 or 6 membered monocyclic heteroaryl ring, which  
25 ring contains 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur,

wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, selected from chloro, fluoro, cyano and (1-3C)alkoxy;

(tt)  $Q^2$  is phenyl, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, as hereinbefore defined in (rr) or (ss);

5 (uu)  $Q^2$  is phenyl, wherein  $Q^2$  optionally bears 1 or 2 substituents, which may be the same or different, selected from chloro and fluoro;

(vv)  $Q^2$  is phenyl, wherein  $Q^2$  bears 1 or 2 substituents, which may be the same or different, selected from chloro and fluoro;

(ww)  $Q^2$  is phenyl, wherein  $Q^2$  bears 1 or 2 (particularly 1) fluoro substituents;

10 (xx)  $Q^2$  is 3-fluorophenyl;

(yy)  $Q^2$  is a 5 or 6 membered monocyclic heteroaryl ring, which ring contains 1 nitrogen heteroatom and optionally 1 additional heteroatom selected from oxygen, nitrogen and sulfur, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, as hereinbefore defined in (rr) or (ss);

15 (zz)  $Q^2$  is selected from phenyl, pyridyl, pyrazinyl, 1,3-thiazolyl, 1H-imidazolyl, 1H-pyrazolyl, 1,3-oxazolyl and isoxazolyl, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, as hereinbefore defined in (rr) or (ss);

(aaa)  $Q^2$  is selected from phenyl, pyridyl, pyrazinyl, 1,3-thiazolyl and isoxazolyl, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or  
20 different, as hereinbefore defined in (rr) or (ss);

(bbb)  $Q^2$  is selected from 2-, 3- or 4-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 3-isoxazolyl, 4-isoxazolyl and 5-isoxazolyl, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, as hereinbefore defined in (rr) or (ss);

25 (ccc)  $Q^2$  is selected from phenyl, 2-pyridyl and 1,3-thiazol-4-yl, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, as hereinbefore defined in (rr) or (ss);

- (ddd)  $Q^2$  is pyridyl (particularly 2-pyridyl or 3-pyridyl, more particularly 2-pyridyl), which optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, as defined above in (rr) or (ss);
- (eee)  $Q^2$  is 2-pyridyl which optionally bears 1 or 2 substituents selected from fluoro, chloro  
5 and (1-2C)alkoxy;
- (fff)  $Q^2$  is 2-pyridyl;
- (ggg)  $Q^2$  is 1,3-thiazolyl (particularly 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl), which optionally bears 1 or 2 substituents (for example 1), which may be the same or different, as defined above in (rr) or (ss);
- 10 (hhh)  $Q^2$  is 1,3-thiazol-4-yl, which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro and (1-2C)alkoxy;
- (iii)  $Q^2$  is 1,3-thiazol-4-yl;
- (ijj)  $Q^2$  is selected from 3-fluorophenyl, 2-pyridyl and 1,3-thiazol-4-yl;
- (kkk)  $Q^2$  is selected from 2-, 3- or 4-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl,  
15 1,3-thiazol-5-yl, 3-isoxazolyl, 4-isoxazolyl and 5-isoxazolyl, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, as hereinbefore defined in (rr) or (ss); and
- $X^3$  is  $C(R^5)_2$  wherein each  $R^5$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl (particularly each  $R^5$  is hydrogen);
- 20 (lll)  $Q^2$  is selected from 2-, 3- or 4-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 3-isoxazolyl, 4-isoxazolyl and 5-isoxazolyl, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, as hereinbefore defined in (rr) or (ss);
- $X^3$  is  $C(R^5)_2$  wherein each  $R^5$ , which may be the same or different, is selected from  
25 hydrogen and (1-2C)alkyl (particularly each  $R^5$  is hydrogen); and
- $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  are all hydrogen; and

(mmm) the group  $-X^3-Q^2$  is selected from pyrid-2-ylmethyl, 1,3-thiazol-4-ylmethyl and 3-fluorobenzyl.

An embodiment of the present invention is a quinazoline derivative of the Formula I wherein:

- 5         $R^1$  is selected from hydrogen and (1-3C)alkoxy (for example  $R^1$  is hydrogen or methoxy, particularly hydrogen);

$X^1$  is selected from a direct bond,  $CH_2$  and  $CH(CH_3)$ ;

$X^3$  is  $CH_2$ ;

- 10         $Q^2$  is aryl or heteroaryl, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, selected from chloro, fluoro, cyano and (1-3C)alkoxy;

and wherein  $X^2$ ,  $Q^1$ , Z,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the values defined hereinbefore;

or a pharmaceutically-acceptable salt thereof.

- 15        In this embodiment a particular value for  $Q^2$  is phenyl or a 5 or 6 membered heteroaryl ring containing 1 nitrogen heteroatom and optionally 1 additional heteroatom independently selected from oxygen, nitrogen and sulfur, and wherein  $Q^2$  optionally bears one or more substituents as defined above.

Another embodiment of the present invention is a quinazoline derivative of the Formula I wherein:

- 20         $R^1$  is selected from hydrogen and (1-3C)alkoxy (for example  $R^1$  is hydrogen or methoxy, particularly hydrogen);

$X^1$  is selected from a direct bond and  $CH_2$ ;

$X^3$  is  $CH_2$ ;

- 25         $Q^2$  is heteroaryl, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents (for example 1 or 2), which may be the same or different, selected from chloro, fluoro, cyano and (1-3C)alkoxy;



and wherein  $X^2$ ,  $Q^1$ ,  $Z$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the values defined hereinbefore;

or a pharmaceutically-acceptable salt thereof.

In this embodiment a particular value for  $Q^2$  is a 5 or 6 membered heteroaryl ring containing 1 nitrogen heteroatom and optionally 1 additional heteroatom independently  
5 selected from oxygen, nitrogen and sulfur, and wherein  $Q^2$  optionally bears one or more substituents as defined above.

Another embodiment of the present invention is a quinazoline derivative of the Formula I wherein:

$R^1$  is selected from hydrogen and (1-3C)alkoxy (for example  $R^1$  is hydrogen or  
10 methoxy, particularly hydrogen);

$X^3$  is  $CH_2$ ;

$Q^2$  is phenyl or a 5 or 6 membered heteroaryl ring containing 1 nitrogen heteroatom and optionally 1 additional heteroatom independently selected from oxygen, nitrogen and sulfur;

15  $X^1$  is selected from  $CH_2$  and  $CH(CH_3)$ ;

$Q^1$  is selected from pyrrolidinyl and piperidinyl, wherein  $Q^1$  optionally bears an oxo substituent and wherein  $Q^1$  is linked to the group  $X^1$  by a ring carbon atom;

$X^2$  is selected from (i)  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-(CR^3R^4)-$ ,  $-(CR^3R^4CH_2)-$  and  $-(CH_2CR^3R^4)$ , wherein each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from  
20 hydrogen and (1-2C)alkyl, provided that  $R^3$  and  $R^4$  are not both hydrogen, or (ii)  $-(CR^3R^4)-$ , wherein  $R^3$  and  $R^4$  together with the carbon atom to which they are attached represent a cyclopropyl ring;

$Z$  is selected from hydroxy, amino and (1-6C)alkylamino;

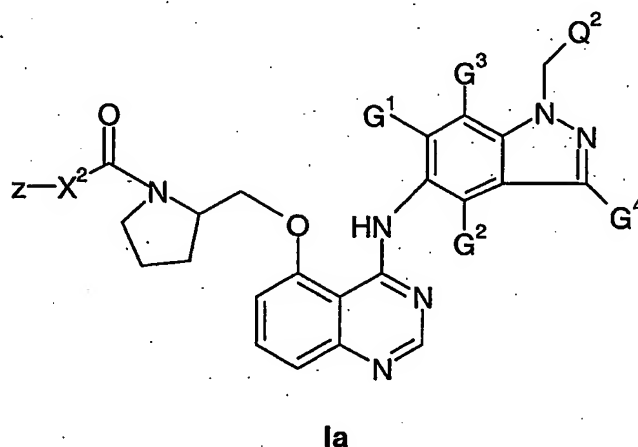
and wherein  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the values defined hereinbefore;

25 or a pharmaceutically-acceptable salt thereof.

In this embodiment a particular value for  $X^1$  is  $CH_2$  and  $Q^1$  is selected from pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-2-yl, piperidinyl-3-yl and piperidin-4-yl. Still more particularly in this embodiment  $X^1$  is  $CH_2$  and  $Q^1$  is selected from pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-2-yl, piperidinyl-3-yl and piperidin-4-yl, and  $Z-X^2$  is hydroxymethyl.

- 5 In this embodiment a particular value for  $Q^2$  is phenyl, pyridyl, pyrazinyl, 1,3-thiazolyl or isoxazolyl, more particularly  $Q^2$  is selected from 2-pyridyl, 3-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl and 3-isoxazolyl, wherein  $Q^2$  optionally bears one or more substituents as defined above.

Another embodiment of the compounds of Formula I is a quinazoline derivative of the  
10 Formula Ia:



wherein:

- $X^2$  is a group of the formula  $-(CR^3R^4)_p-$ , wherein (i)  $p$  is 1, 2 or 3 and each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl, or (ii)  $p$  is  
15 1 and  $R^3$  and  $R^4$  together with the carbon atom to which they are attached represent a cyclopropyl ring; and

$G^1, G^2, G^3, G^4, Q^2$  and  $Z$  are as hereinbefore defined in relation to Formula I;

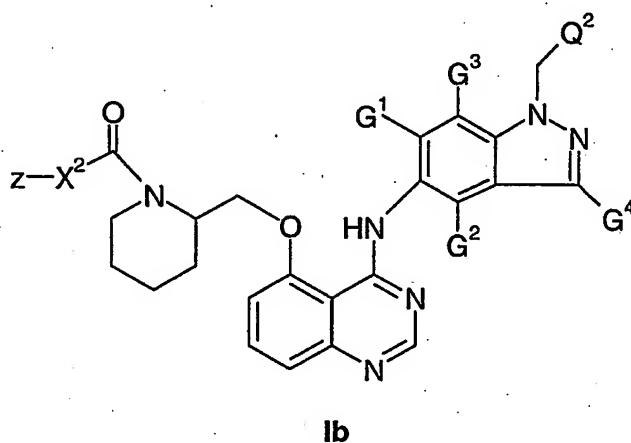
or a pharmaceutically-acceptable salt thereof.

- In this embodiment a particular value for  $X^2$  is  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-(CR^3R^4)-$ ,  
20  $-(CR^3R^4CH_2)-$  or  $-(CH_2CR^3R^4)-$ , wherein each of  $R^3$  and  $R^4$ , which may be the same or

different, is selected from hydrogen and (1-2C)alkyl (particularly from hydrogen and methyl), provided that  $R^3$  and  $R^4$  are not both hydrogen. Another particular value for  $X^2$  is  $-(CR^3R^4)-$ , wherein  $R^3$  and  $R^4$  together with the carbon atom to which they are attached represent a cyclopropyl ring. More particularly, in this embodiment,  $X^2$  is  $-CH_2-$ .

5 A particular value for Z in this embodiment is hydroxy.

A further particular embodiment of the compounds of Formula I is a quinazoline derivative of the Formula Ib:



wherein:

10  $X^2$  is a group of the formula  $-(CR^3R^4)_p-$ , wherein (i) p is 1, 2 or 3 and each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl, or (ii) p is 1 and  $R^3$  and  $R^4$  together with the carbon atom to which they are attached represent a cyclopropyl ring; and

$G^1$ ,  $G^2$ ,  $G^3$ ,  $G^4$ ,  $Q^2$  and Z are as hereinbefore defined in relation to Formula I;

15 or a pharmaceutically-acceptable salt thereof.

In this embodiment a particular value for  $X^2$  is  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-(CR^3R^4)-$ ,  $-(CR^3R^4CH_2)-$  or  $-(CH_2CR^3R^4)-$ , wherein each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl (particularly from hydrogen and methyl), provided that  $R^3$  and  $R^4$  are not both hydrogen. Another particular value for  $X^2$  is  $-(CR^3R^4)-$ ,

wherein R<sup>3</sup> and R<sup>4</sup> together with the carbon atom to which they are attached represent a cyclopropyl ring. More particularly, in this embodiment, X<sup>2</sup> is -CH<sub>2</sub>-.

A particular value for Z in this embodiment is hydroxy.

Particular compounds of the invention are, for example, one or more quinazoline  
5 derivatives of the Formula I selected from:

2-oxo-2-((2R)-2-{[(4-{[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]amino}quinazolin-5-yl)oxy]methyl}pyrrolidin-1-yl)ethanol;

2-oxo-2-((2R)-2-{[(4-{[1-(1,3-thiazol-4-ylmethyl)-1H-indazol-5-yl]amino}quinazolin-5-yl)oxy]methyl}pyrrolidin-1-yl)ethanol;

10 2-((2R)-2-{[(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}quinazolin-5-yl)oxy]methyl}pyrrolidin-1-yl)-2-oxoethanol;

2-oxo-2-((2R)-2-{[(4-{[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]amino}quinazolin-5-yl)oxy]methyl}piperidin-1-yl)ethanol; and

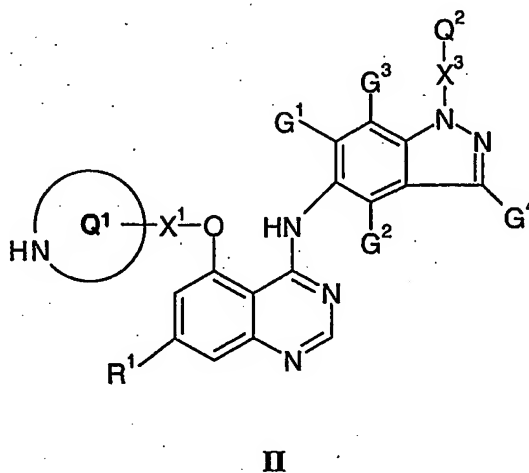
2-oxo-2-((2R)-2-{[(4-{[1-(1,3-thiazol-4-ylmethyl)-1H-indazol-5-yl]amino}quinazolin-5-yl)oxy]methyl}piperidin-1-yl)ethanol;  
15

or a pharmaceutically-acceptable salt thereof.

A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes include, for example, those illustrated in  
20 International Patent Applications WO 96/15118, WO 01/94341, WO 03/040108 and WO 03/040109. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, R<sup>1</sup>, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, Q<sup>1</sup>, Q<sup>2</sup>, G<sup>1</sup>, G<sup>2</sup>, G<sup>3</sup>, G<sup>4</sup> and Z have any of the meanings defined hereinbefore. Necessary starting materials  
25 may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials

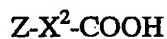
are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Process (a) The coupling, conveniently in the presence of a suitable base, of a quinazoline of the Formula II:



wherein  $R^1$ ,  $X^1$ ,  $X^3$ ,  $Q^1$ ,  $Q^2$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a carboxylic acid of the Formula III, or a reactive derivative thereof:

10

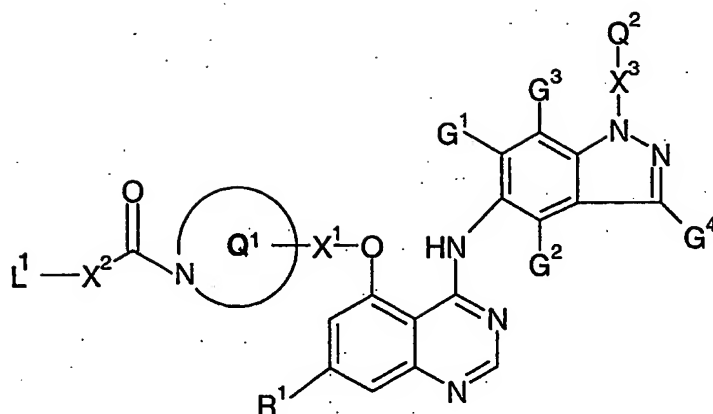


III

wherein Z and  $X^2$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

15 Process (b) The coupling of a quinazoline of the Formula IV:



IV

wherein  $L^1$  is a suitable displaceable group and  $R^1$ ,  $X^1$ ,  $X^2$ ,  $X^3$ ,  $Q^1$ ,  $Q^2$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the meanings defined hereinbefore except that any functional group is

5 protected if necessary, with a compound of the Formula V:

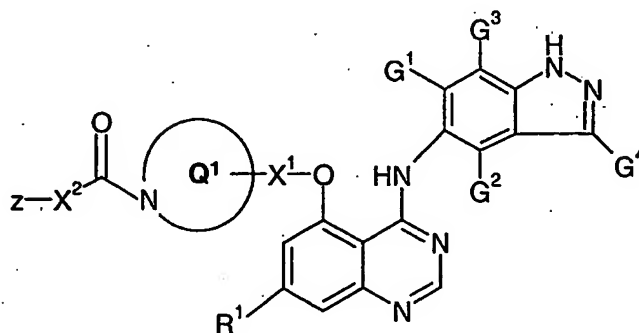


V

wherein Z has any of the meanings defined hereinbefore except that any functional group is protected if necessary;

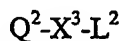
10 or

Process (c) The coupling, conveniently in the presence of a suitable base, of a quinazoline of the Formula VI:



VI

wherein  $R^1$ ,  $X^1$ ,  $X^2$ ,  $Z$ ,  $Q^1$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula VII:



5

VII

wherein  $L^2$  is a suitable displaceable group and  $Q^2$  and  $X^3$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

and thereafter, if necessary:

(i) converting a quinazoline derivative of the Formula I into another quinazoline derivative of the Formula I;

(ii) removing any protecting group that is present by conventional means;

(iii) forming a pharmaceutically-acceptable salt.

Specific conditions for the above reactions are as follows:

#### Process (a)

#### 15 Reaction Conditions for Process (a)

As the skilled person would appreciate, the coupling reaction may, if necessary, conveniently be carried out in the presence of a suitable coupling agent, such as a carbodiimide, or a suitable peptide coupling agent, for example O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate (HATU) or a carbodiimide such as dicyclohexylcarbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine.

The coupling reaction is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline

25

earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate.

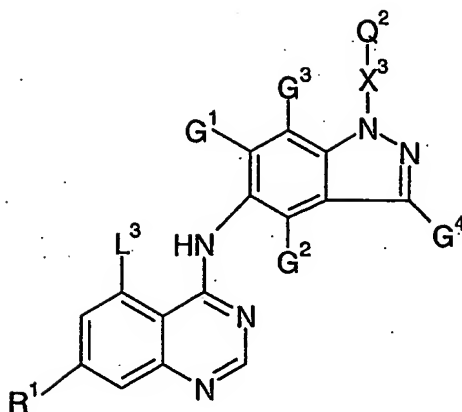
The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ester such as ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, from 0 to 120°C, conveniently at or near ambient temperature.

10 By the term "reactive derivative" of a carboxylic acid of the Formula **III** is meant a carboxylic acid derivative that will react with a quinazoline of the Formula **II** to give the corresponding amide. A suitable reactive derivative of a carboxylic acid of the Formula **III** is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example  
15 an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as methanol, ethanol, isopropanol, butanol or N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and azide such as  
20 diphenylphosphoryl azide; or an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide. The reaction of such reactive derivatives of carboxylic acid with amines (such as a compound of the Formula **II**) is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may  
25 conveniently be performed at a temperature as described above.

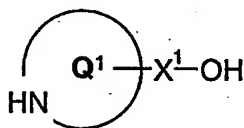
#### Preparation of Starting Materials for Process (a)

A quinazoline of the Formula **II** may be obtained by conventional procedures. For example, a quinazoline of the Formula **II** may be obtained by the reaction, conveniently in the presence of a suitable base, of a quinazoline of the Formula **IIa**:



**IIa**

wherein  $R^1$ ,  $X^3$ ,  $Q^2$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary, and  $L^3$  is a suitable displaceable  
 5 group, with an alcohol of the Formula **IIb**:

**IIb**

wherein  $Q^1$  and  $X^1$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary; and thereafter, if necessary removing any  
 10 protecting group that is present by conventional means.

A suitable displaceable group  $L^3$  in a quinazoline of the Formula **IIa** is, for example, halogeno or a sulfonyloxy group, for example fluoro, chloro, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular displaceable group  $L^3$  is fluoro or chloro, more particularly fluoro.

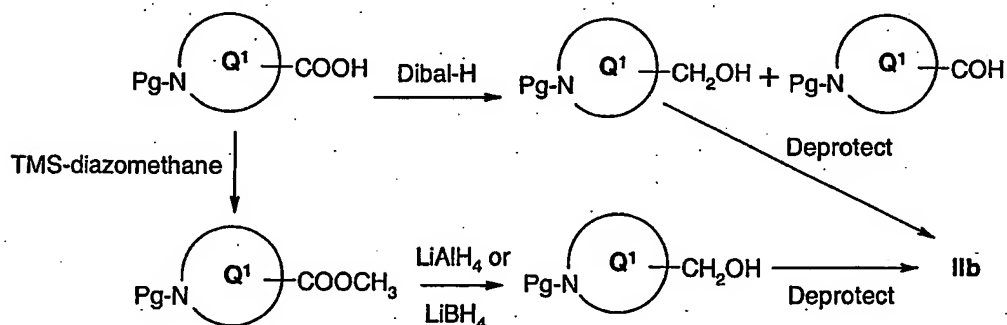
15 A suitable base for the reaction of a quinazoline of the Formula **IIa** and an alcohol of the Formula **IIb** includes, for example a strong non-nucleophilic base such as an alkali metal hydride, for example sodium hydride, or an alkali metal amide, for example lithium di-isopropylamide (LDA).

The reaction of a quinazoline of the Formula **IIa** and an alcohol of the Formula **IIb** is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range of, for example, 10 to 250°C, preferably in the range 40 to 150°C. Conveniently, this reaction may also be performed by heating the reactants in a sealed vessel using a suitable heating apparatus such as a microwave heater.

10 Conveniently, the reaction of a quinazoline of the Formula IIa and an alcohol of the Formula IIb is performed in the presence of a suitable catalyst, for example a crown ether such as 15-crown-5.

Alcohols of the Formula **IIb** are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

15 For example, alcohols of the Formula **IIb** wherein  $X^1$  is  $CH_2$  may be prepared by the reduction of the corresponding acid or ester thereof as illustrated in *Reaction Scheme 1*:



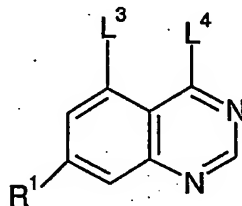
### Reaction Scheme 1

wherein Q<sup>1</sup> has any of the meanings defined hereinbefore, Pg represents a suitable  
20 protecting group, TMS represents trimethylsilane and Dibal-H represents  
diisobutylaluminium hydride;

In *Reaction Scheme 1*, the protection with TMS-diazomethane may conveniently be carried out in the presence of methanol, optionally in the presence of a suitable inert solvent or diluent, and at a temperature of about 25°C.

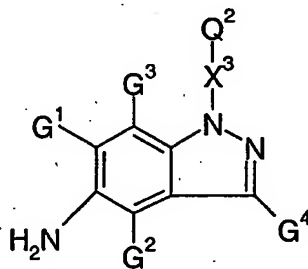
In *Reaction Scheme 1*, the reaction with DiBal-H, LiAlH<sub>4</sub> or LiBH<sub>4</sub> may conveniently  
5 be carried out in the presence of a suitable inert solvent or diluent, such as diethyl ether or tetrahydrofuran, and at a temperature in the range, for example, -78 to 60°C.

A quinazoline of the Formula IIa may be obtained by conventional procedures. For example, a quinazoline of the Formula IIc:



IIc

wherein R<sup>1</sup> has any of the meanings defined hereinbefore and L<sup>3</sup> and L<sup>4</sup> are  
displaceable groups, and L<sup>4</sup> is more labile than L<sup>3</sup>, may be reacted with a compound of the  
Formula IId:



IId

wherein X<sup>3</sup>, Q<sup>2</sup>, G<sup>1</sup>, G<sup>2</sup>, G<sup>3</sup> and G<sup>4</sup> have any of the meanings defined hereinbefore  
except that any functional group is protected if necessary, whereafter any protecting group  
that is present is removed by conventional means.

A suitable displaceable group  $L^3$  is as hereinbefore defined, particularly fluoro. A suitable displaceable group  $L^4$  is, for example, a halogeno (particularly chloro), alkoxy, aryloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, alkylsulfonyloxy or arylsulfonyloxy group, for example a chloro, bromo, methoxy, phenoxy, 5 pentafluorophenoxy, methylthio, methanesulfonyl, methanesulfonyloxy or toluene-4-sulfonyloxy group.

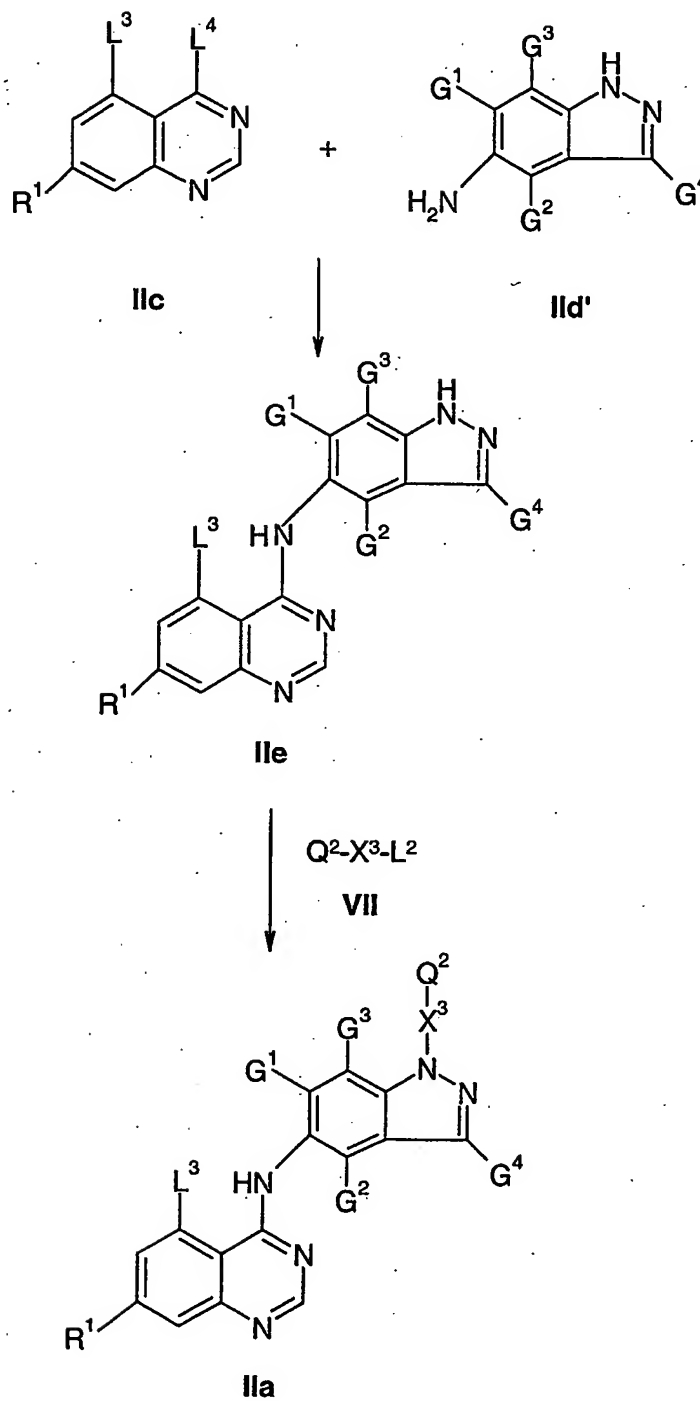
The reaction of a quinazoline of Formula **IIc** with a compound of Formula **IIId** may conveniently be carried out in the presence of an acid. Suitable acids include, for example hydrogen chloride gas (conveniently dissolved in diethyl ether or dioxane) or hydrochloric 10 acid.

Alternatively, the reaction of a quinazoline of the Formula **IIc** with a compound of the Formula **IIId** may be carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or 15 diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, such as sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate, or, for example, an alkali metal hydride, such as sodium hydride.

Alternatively, a quinazoline of the Formula **IIc**, wherein  $L^4$  is halogeno (for example chloro) may be reacted with a compound of the Formula **IIId** in the absence of an acid or a 20 base. In this reaction displacement of the halogeno leaving group  $L^4$  results in the formation of the acid  $HL^4$  in-situ and the autocatalysis of the reaction.

The above reactions are conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon 25 tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The above reactions are conveniently carried out at a temperature in the range, for example, 0 to 250°C, conveniently in the range 40 to 80°C or, preferably, at or near the reflux temperature of the 30 solvent when used.

Alternatively, a quinazoline of the Formula IIa may be obtained as illustrated in *Reaction Scheme 2*:



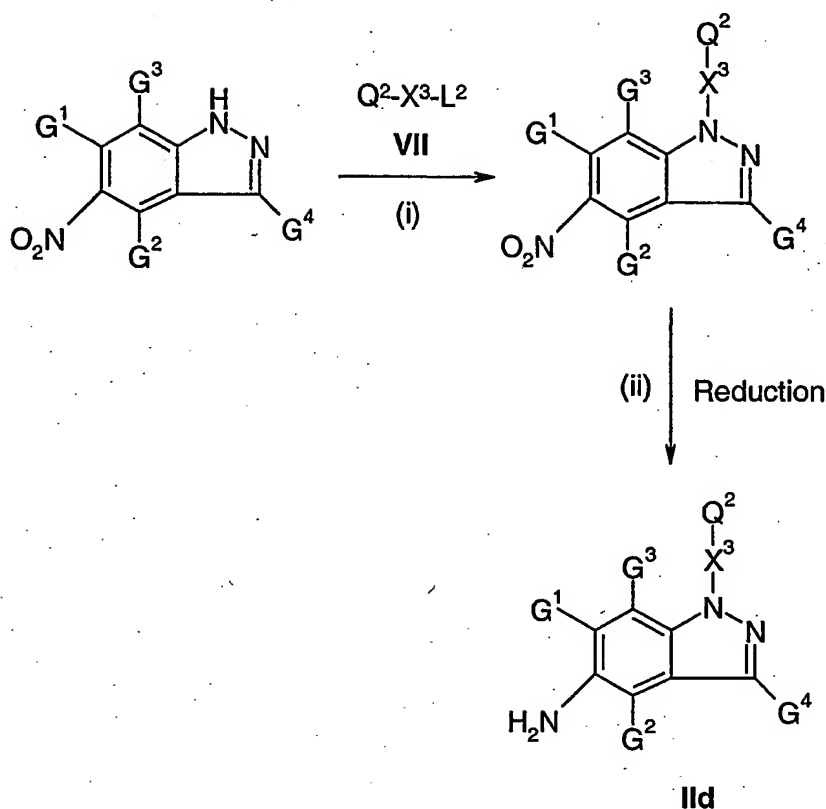
*Reaction Scheme 2*

wherein  $L^2$ ,  $L^3$  and  $L^4$  are suitable displaceable groups and  $R^1$ ,  $X^3$ ,  $Q^2$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

- 5 In *Reaction Scheme 2*, a suitable displaceable group  $L^2$  in the compound of the Formula **VII** is, for example, halogeno or a sulfonyloxy group, for example fluoro, chloro, bromo, iodo, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular group  $L^2$  is bromo, chloro or methylsulfonyloxy. The suitable displaceable groups  $L^3$  and  $L^4$  are as hereinbefore defined.
- 10 The reaction of a compound of the Formula **IIc** and a compound of the Formula **IIId'** is conveniently carried out using analogous conditions to those discussed above for the reaction of a quinazoline of the Formula **IIc** and a compound of the Formula **IIId**. The reaction of a compound of the Formula **IIe** and a compound of the Formula **VII** is conveniently carried out using analogous conditions to those discussed below for Process (c).
- 15 A quinazoline of the Formula **IIc** may be obtained using conventional methods, for example, when  $R^1$  is hydrogen,  $L^3$  is fluoro and  $L^4$  is halogeno, 5-fluoro-3,4-dihydroquinazolin-4-one may be reacted with a suitable halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine. The 5-fluoro-3,4-dihydroquinazoline starting material is commercially
- 20 available or can be prepared using conventional methods, for example as described in J. Org. Chem. 1952, 17, 164-176.

Compounds of the Formula **IIId** and **IIId'** are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art. For example, compounds of the Formula **IIId** may be prepared as illustrated in

25 *Reaction Scheme 3*:



Reaction Scheme 3

wherein  $L^2$  is a suitable displaceable group as defined below and  $X^3$ ,  $Q^2$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the meanings defined hereinbefore except that any functional group is  
 5 protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction of step (i) in *Reaction Scheme 3* is conveniently carried out using analogous conditions to those discussed below for Process (c).

The reduction in step (ii) in *Reaction Scheme 3* may be conducted using conventional  
 10 methods. For example, the reduction of the nitro group in step (ii) may be carried out under standard conditions, for example by catalytic hydrogenation over a platinum/carbon, palladium/carbon or nickel catalyst, treatment with a metal such as iron, titanium (III) chloride, tin (II) chloride or indium, or treatment with another suitable reducing agent such as sodium dithionite or a platinum (IV) oxide.

Process (b)Reaction Conditions for Process (b)

A suitable displaceable group  $L^1$  in a compound of the Formula IV is for example halogeno or a sulfonyloxy group, for example fluoro, chloro, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular displaceable group  $L^1$  is fluoro, chloro or methylsulfonyloxy.

The reaction of a quinazoline of the Formula IV with a compound of the Formula V is conveniently carried out in the presence of a suitable catalyst such as, for example, tetra-n-butylammonium iodide or potassium iodide.

The reaction of a quinazoline of the Formula IV and a compound of the Formula V is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range of, for example, from 25 to 150°C, conveniently at about 100°C.

15 Preparation of Starting Materials for Process (b)

A quinazoline of the Formula IV may be prepared using conventional methods, for example, as discussed above.

Compounds of the Formula V are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

20 Process (c)Reaction Conditions for Process (c)

A suitable displaceable group  $L^2$  in the compound of the Formula VII is, for example, halogeno or a sulfonyloxy group, for example fluoro, chloro, bromo, iodo, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular displaceable group  $L^2$  is bromo, chloro or methylsulfonyloxy.



The reaction of a quinazoline of the Formula VI with a compound of the Formula VII is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or

5 diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, such as sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate, or, for example, an alkali metal hydride, such as sodium hydride.

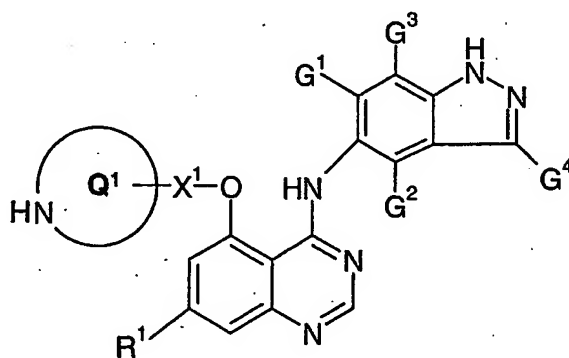
The reaction of a quinazoline of the Formula VI with a compound of the Formula VII is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a

10 halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide; N-methylpyrrolidin-2-one or dimethylsulfoxide. Alternatively, the reaction may be conducted in the absence of an inert solvent or diluent. The reaction is conveniently carried out at a

15 temperature in the range of, for example, from 25 to 100°C, conveniently at or near ambient temperature.

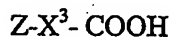
#### Preparation of Starting Materials for Process (c)

A quinazoline of the Formula VI may be prepared using conventional methods, for example, by reacting a compound of the Formula VIa:



VIa

wherein  $R^1$ ,  $Q^1$ ,  $X^1$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  are as hereinbefore defined except that any functional group is protected if necessary, with a carboxylic acid of the Formula III, or a reactive derivative thereof:



5

## III

wherein Z and  $X^3$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary and whereafter any protecting group that is present is removed by conventional means.

The reaction of a quinazoline of the Formula VIa and a compound of the Formula III  
10 is conveniently carried using analogous conditions to those described above for Process (a).

Compounds of the Formula VII are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

The quinazoline derivative of the Formula I may be obtained from the above processes in the form of the free base or alternatively it may be obtained in the form of a salt, for  
15 example an acid addition salt. When it is desired to obtain the free base from a salt of the compound of Formula I, the salt may be treated with a suitable base, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or by treatment with ammonia for example using a methanolic ammonia solution such as 7N ammonia in  
20 methanol.

The protecting groups used in the processes above may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or  
25 known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1 to 4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are  
5 given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1 to 20 carbon atoms). Examples of carboxy protecting groups include straight or  
10 branched chain (1 to 12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and  
15 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example  
20 acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl  
25 groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and  
30 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example

allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); lower alkanoyloxyalkyl groups (for example pivaloyloxymethyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methyldiene) and  
5 benzyldiene and substituted benzyldiene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl. For example a tert butoxycarbonyl protecting  
10 group may be removed from an amino group by an acid catalysed hydrolysis using trifluoroacetic acid.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2<sup>nd</sup> Edition, by T. Green *et al.*, also  
15 published by John Wiley & Son, for general guidance on protecting groups.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of  
20 the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the  
25 introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I  
30 is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

As mentioned hereinbefore some of the compounds according to the present invention may contain one or more chiral centers and may therefore exist as stereoisomers.

Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of a racemate for  
5 example by fractional crystallisation, resolution or HPLC. The diastereoisomers may be isolated by separation by virtue of the different physical properties of the diastereoisomers, for example, by fractional crystallisation, HPLC or flash chromatography. Alternatively particular stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a  
10 chiral reagent. When a specific stereoisomer is isolated it is suitably isolated substantially free for other stereoisomers, for example containing less than 20%, particularly less than 10% and more particularly less than 5% by weight of other stereoisomers.

In the section above relating to the preparation of the quinazoline derivative of Formula I, the expression "inert solvent" refers to a solvent which does not react with the  
15 starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the  
20 individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

Certain intermediates used in the processes described above are novel and form a further feature of the present invention. Accordingly there is provided a compound selected  
25 from a compound the Formulae II, IV and VI as hereinbefore defined, or a salt thereof. The intermediate may be in the form of a salt of the intermediate. Such salts need not be a pharmaceutically-acceptable salt. For example it may be useful to prepare an intermediate in the form of a pharmaceutically non-acceptable salt if, for example, such salts are useful in the manufacture of a compound of Formula I.

30 Particular intermediate compounds of the invention are, for example, one or more compounds of the Formula II selected from:

N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-amine;

5-[(2R)-pyrrolidin-2-ylmethoxy]-N-[1-(1,3-thiazol-4-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine;

5 N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-amine; and

5-[(2R)-piperidin-2-ylmethoxy]-N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine;

or a salt thereof.

#### 10 Biological Assays

The inhibitory activities of compounds were assessed in non-cell based protein tyrosine kinase assays as well as in cell based proliferation assays before their *in vivo* activity was assessed in Xenograft studies.

##### a) Protein Tyrosine Kinase phosphorylation Assays

15 This test measures the ability of a test compound to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by EGFR, erbB2 and erbB4 tyrosine kinase enzyme.

Recombinant intracellular fragments of EGFR, erbB2 and erbB4 (accession numbers X00588, X03363 and L07868 respectively) were cloned and expressed in the baculovirus/Sf21 system. Lysates were prepared from these cells by treatment with ice-cold  
20 lysis buffer (20mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) pH7.5, 150mM NaCl, 10% glycerol, 1% Triton X-100, 1.5mM MgCl<sub>2</sub>, 1mM ethylene glycol-bis(β-aminoethyl ether) N',N',N',N'-tetraacetic acid (EGTA), plus protease inhibitors and then cleared by centrifugation.

Constitutive kinase activity of these recombinant proteins was determined by their  
25 ability to phosphorylate a synthetic peptide (made up of a random co-polymer of Glutamic Acid, Alanine and Tyrosine in the ratio of 6:3:1). Specifically, Maxisorb™ 96-well immunoplates were coated with synthetic peptide (0.2μg of peptide in a 100μl phosphate

buffered saline (PBS) solution and incubated at 4°C overnight). Plates were washed in 50mM HEPES pH 7.4 at room temperature to remove any excess unbound synthetic peptide. EGFR or erbB2 activities were assessed by incubation in peptide coated plates for 20 minutes at room temperature in 50mM HEPES pH 7.4 at room temperature, adenosine trisphosphate (ATP) at Km concentration for the respective enzyme, 10mM MnCl<sub>2</sub>, 0.05mM Na<sub>3</sub>VO<sub>4</sub>, 0.1mM DL-dithiothreitol (DTT), 0.05% Triton X-100 with test compound in DMSO (final concentration of 2.5%). Reactions were terminated by the removal of the liquid components of the assay followed by washing of the plates with PBS-T (phosphate buffered saline with 0.05% Tween 20).

- 10 The immobilised phospho-peptide product of the reaction was detected by immunological methods. Firstly, plates were incubated for 90 minutes at room temperature with anti-phosphotyrosine primary antibodies that were raised in the mouse (4G10 from Upstate Biotechnology). Following extensive washing, plates were treated with Horseradish Peroxidase (HRP) conjugated sheep anti-mouse secondary antibody (NXA931 from Amersham) for 60 minutes at room temperature. After further washing, HRP activity in each well of the plate was measured colorimetrically using 22'-Azino-di-[3-ethylbenzthiazoline sulfonate (6)] diammonium salt crystals (ABTS™ from Roche) as a substrate.

- Quantification of colour development and thus enzyme activity was achieved by the measurement of absorbance at 405nm on a Molecular Devices ThermoMax microplate reader.
- 20 Kinase inhibition for a given compound was expressed as an IC<sub>50</sub> value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of phosphorylation in this assay. The range of phosphorylation was calculated from the positive (vehicle plus ATP) and negative (vehicle minus ATP) control values.

#### **b) EGFR driven KB cell proliferation assay**

- 25 This assay measures the ability of a test compound to inhibit the proliferation of human tumour cell line, KB (obtained from the American Type Culture Collection (ATCC)).

- KB cells were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% foetal calf serum, 2 mM glutamine and non-essential amino acids at 37°C in a 7.5% CO<sub>2</sub> air incubator. Cells were harvested from the stock flasks using Trypsin / ethylenediaminetetraacetic acid (EDTA). Cell density was measured using a
- 30

haemocytometer and viability was calculated using trypan blue solution before being seeded at a density of  $1.25 \times 10^3$  cells per well of a 96 well plate in DMEM containing 2.5% charcoal stripped serum, 1mM glutamine and non-essential amino acids at 37°C in 7.5% CO<sub>2</sub> and allowed to settle for 4 hours.

- 5        Following adhesion to the plate, the cells are treated with or without EGF (final concentration of 1ng/ml) and with or without compound at a range of concentrations in dimethylsulfoxide (DMSO) (0.1% final) before incubation for 4 days. Following the incubation period, cell numbers were determined by addition of 50µl of 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (stock 5mg/ml) for 2 hours.
- 10    MTT solution was then tipped off, the plate gently tapped dry and the cells dissolved upon the addition of 100µl of DMSO.

Absorbance of the solubilised cells was read at 540nm using a Molecular Devices ThermoMax microplate reader. Inhibition of proliferation was expressed as an IC<sub>50</sub> value. This was determined by calculation of the concentration of compound that was required to

15    give 50% inhibition of proliferation. The range of proliferation was calculated from the positive (vehicle plus EGF) and negative (vehicle minus EGF) control values.

**c)    Clone 24 phospho-erbB2 cell assay**

- This immunofluorescence end point assay measures the ability of a test compound to inhibit the phosphorylation of erbB2 in a MCF7 (breast carcinoma) derived cell line which
- 20    was generated by transfecting MCF7 cells with the full length erbB2 gene using standard methods to give a cell line that overexpresses full length wild type erbB2 protein (hereinafter 'Clone 24' cells).

Clone 24 cells were cultured in Growth Medium (phenol red free Dulbecco's modified Eagle's medium (DMEM) containing 10% foetal bovine serum, 2 mM glutamine

25    and 1.2mg/ml G418) in a 7.5% CO<sub>2</sub> air incubator at 37°C. Cells were harvested from T75 stock flasks by washing once in PBS (phosphate buffered saline, pH7.4, Gibco No. 10010-015) and harvested using 2mls of Trypsin (1.25mg/ml) / ethylenediaminetetraacetic acid (EDTA) (0.8mg/ml) solution. The cells were resuspended in Growth Medium. Cell density was measured using a haemocytometer and viability was calculated using Trypan Blue



solution before being further diluted in Growth Medium and seeded at a density of  $1 \times 10^4$  cells per well (in 100 $\mu$ l) into clear bottomed 96 well plates (Packard, No. 6005182).

3 days later, Growth Medium was removed from the wells and replaced with 100 $\mu$ l Assay Medium (phenol red free DMEM, 2mM glutamine, 1.2mg/ml G418) either with or  
5 without erbB inhibitor compound. Plates were returned to the incubator for 4 hours and then 20 $\mu$ l of 20% formaldehyde solution in PBS was added to each well and the plate was left at room temperature for 30 minutes. This fixative solution was removed with a multichannel pipette, 100 $\mu$ l of PBS was added to each well and then removed with a multichannel pipette and then 50 $\mu$ l PBS was added to each well. Plates were then sealed and stored for up to 2  
10 weeks at 4°C.

Immunostaining was performed at room temperature. Cells were washed once with 200 $\mu$ l PBS / Tween 20 (made by adding 1 sachet of PBS / Tween dry powder (Sigma, No. P3563) to 1L of double distilled H<sub>2</sub>O) using a plate washer, then 100 $\mu$ l of 0.5% Triton X-100 / PBS was added to each well to permeabilise the cells. After 10 minutes, the plates were  
15 washed with 200 $\mu$ l PBS / Tween 20 and then 100 $\mu$ l Blocking Solution (5% Marvel dried skimmed milk (Nestle) in PBS) was added per well and the plates were incubated for 15 minutes. Following removal of the Blocking Solution with a plate washer, 30 $\mu$ l of rabbit polyclonal anti-phospho erbB2 IgG antibody (epitope phospho-Tyr 1248, SantaCruz, No. SC-12352-R), diluted 1:250 in Blocking Solution, was added to each well and incubated for 2  
20 hours. Then this primary antibody solution was removed from the wells using a plate washer followed by two 200 $\mu$ l PBS / Tween 20 washes using a plate washer. 100 $\mu$ l of Blocking solution was added per well and the plates were incubated for 10 minutes. Then 30 $\mu$ l of Alexa-Fluor 488 goat anti-rabbit IgG secondary antibody (Molecular Probes, No. A-11008), diluted 1:750 in Blocking Solution, was added to each well. From now onwards, wherever  
25 possible, plates were protected from light exposure, at this stage by sealing with black backing tape. The plates were incubated for 45 minutes and then the secondary antibody solution was removed from the wells followed by three 200 $\mu$ l PBS / Tween 20 washes using a plate washer. Then 100 $\mu$ l PBS was added to each plate, incubated for 10 minutes and then removed using a plate washer. Then 50 $\mu$ l of PBS was added to each well and plates were  
30 resealed with black backing tape and stored at 4°C before analysis. Plates were analysed within six hours of completing the immunostaining.

The Fluorescence signal in each well was measured using an Acumen Explorer Instrument (Acumen Bioscience Ltd.), a plate reader that can be used to rapidly quantitate features of images generated by laser-scanning. The instrument was set to measure the number of fluorescent objects above a pre-set threshold value and this provided a measure of the phosphorylation status of erbB2 protein. Fluorescence dose response data obtained with each compound was exported into a suitable software package (such as Origin) to perform curve fitting analysis. Inhibition of erbB2 phosphorylation was expressed as an IC<sub>50</sub> value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of erbB2 phosphorylation signal.

#### 10 d) *In vivo* BT474C Xenograft assay

This assay measures the ability of a test compound to inhibit the growth of a specific variant of the BT-474 tumour cell line grown as a xenograft in Female Swiss athymic mice (Alderley Park, *nu/nu* genotype) (Baselga, J. *et al.* (1998) *Cancer Research*, **58**, 2825-2831).

The BT-474 tumour cell line (human mammary carcinoma) was obtained from Dr Baselga (at Laboratorio Recerca Oncologica, Paseo Vall D'Hebron 119-129, Barcelona 08035, Spain). This cell line was subcloned and a certain population (hereinafter referred to as "BT474C") was obtained.

Female Swiss athymic (*nu/nu* genotype) mice were bred and maintained in Alderley Park in negative pressure Isolators (PFI Systems Ltd.). Mice were housed in a barrier facility with 12 hour light/dark cycles and provided with sterilised food and water *ad libitum*. All procedures were performed on mice of at least 8 weeks of age. BT474C tumour cell xenografts were established in the hind flank of donor mice by sub-cutaneous injections of  $1 \times 10^7$  freshly cultured cells in 100 $\mu$ l of serum free media with 50% Matrigel per animal. Animals were supplemented with oestradiol benzoate (Mesalin, Intravet UK 0.2 mg/ml), 100 $\mu$ g/animal injected subcutaneously on the day before cell implant, with subsequent weekly boosts of 50 $\mu$ g/animal. On day 14 post-implant, mice were randomised into groups of 10 prior to the treatment with compound or vehicle control that was administered once daily at 0.1ml/10g body weight. Tumour volume was assessed twice weekly by bilateral Vernier calliper measurement, using the formula  $(\text{length} \times \text{width}) \times \sqrt{(\text{length} \times \text{width}) \times (\pi/6)}$ , where length was the longest diameter across the tumour, and width was the corresponding

perpendicular. Growth inhibition from start of treatment was calculated by comparison of the mean changes in tumour volume for the control and treated groups, and statistical significance between the two groups was evaluated using a Students *t* test.

**e) BT474C Cell Proliferation Assay**

5 BT474C cells are a sub-cloned population of *in vivo* competent cells, as discussed above.

The BT474C assay is a MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt – Promega G1111) endpoint-based cell proliferation assay, which measures the ability of a test compound to  
10 inhibit the proliferation of cells over a four-day period. Cells are grown to logarithmic phase in growth media (phenol red free Dulbecco's modified Eagle's medium (DMEM) containing 10% foetal bovine serum, 10% M1 supplement (AstraZeneca internal supply), 1% oxaloacetic acid in a 7.5% CO<sub>2</sub> air incubator at 37°C. Cells are harvested from stock flasks by washing once in PBS (phosphate buffered saline, pH7.4, Gibco No. 10010-015) and removed using  
15 2mls of Trypsin (1.25mg/ml) / ethylenediaminetetraacetic acid (EDTA) (0.8mg/ml) solution. The cells are re-suspended in assay media (phenol red free Dulbecco's modified Eagle's medium (DMEM) containing 10% charcoal/Dextran stripped foetal bovine serum, 10% M1 supplement, 1% oxaloacetic acid. Cell density is measured using a haemocytometer and viability is calculated using Trypan Blue solution before being further diluted in Assay  
20 Medium and seeded at a density of  $1 \times 10^4$  cells per well (in 100ul) into clear bottomed 96 well plates (Costar 3598). One extra plate is set up to act as a Day 0 control plate.

4 hours later, assay medium containing test compound, serially diluted in 100% DMSO (Sigma D5879), in the form of a dose response is added across the plate in triplicate. The Day 0 plate is treated with MTS solution (Tetrazolium compound – made from MTS  
25 powder in a Phenazine ethosulfate (PES - Sigma P4544)/PBS) and incubated for 2 hours before the reaction is stopped by the addition of 10% SDS. The plate is read at 490nm on a spectrophotometer.

Assay plates are left at 37°C for 4 days and then treated with MTS solution (as above), which is converted to a soluble formazan product by active cells. After incubating the plates  
30 for 2 hours the reaction is stopped by the addition of 10% SDS (Sodium dodecyl sulphate)

and the plates are read at 490nm on a spectrophotometer giving absorbance values relative to the concentration of converted dye.

Absorbance dose response data obtained with each compound is exported into a suitable software package (such as Origin) to perform curve-fitting analysis. Inhibition of  
5 BT474C cell proliferation is expressed as an  $IC_{50}$  value (calculated as GI50 by use of a log/lin plot – analyzing data above the day 0 absorbance values). This is determined by calculation of the concentration of compound that is required to give 50% inhibition of cell proliferation.

#### f) hERG-encoded Potassium Channel Inhibition Assay

##### Cell culture for IonWorks™ HT:

10 The hERG-expressing Chinese hamster ovary K1 (CHO) cells described by Persson *et al.* (Persson, F., Carlsson, L., Duker, G., and Jacobson, I., Blocking characteristics of hERG, hNav1.5, and hKvLQT1/hminK after administration of the novel anti-arrhythmic compound AZD7009., J Cardiovasc. Electrophysiol., 16, 329-341.2005) were grown to semi-confluence at 37°C in a humidified environment (5% CO<sub>2</sub>) in F-12 Ham medium containing L-glutamine,  
15 10% foetal calf serum (FCS) and 0.6 mg/ml hygromycin (all Sigma). Prior to use, the monolayer was washed using a pre-warmed (37°C) 3ml aliquot of Versene 1:5,000 (Invitrogen). After aspiration of this solution the flask was incubated at 37°C in an incubator with a further 2 ml of Versene 1:5,000 for a period of 6 minutes. Cells were then detached from the bottom of the flask by gentle tapping and 10 ml of Dulbecco's-PBS containing  
20 calcium (0.9 mM) and magnesium (0.5 mM) (PBS; Invitrogen) was then added to the flask and aspirated into a 15 ml centrifuge tube prior to centrifugation (50 g, for 4 minutes). The resulting supernatant was discarded and the pellet gently re-suspended in 3 ml of PBS. A 0.5 ml aliquot of cell suspension was removed to determine viable cell number based on trypan blue exclusion (Cedex; Innovatis) and the cell re-suspension volume adjusted with PBS to  
25 give the desired final cell concentration. CHO-Kv1.5 cells, which were used to adjust the voltage offset on IonWorks™ HT, were maintained and prepared for use in the same way.

##### IonWorks™ HT electrophysiology:

The principles and operation of this device have been described by Schroeder *et al.* (Schroeder, K., Neagle, B., Trezise, D. J., and Worley, J., Ionworks HT: a new high-

throughput electrophysiology measurement platform, J Biomol Screen, 8, 50-64, 2003).

Briefly, the technology is based on a 384-well plate (PatchPlate™) in which a recording is attempted in each well by using suction to position and hold a cell on a small hole separating two isolated fluid chambers. Once sealing has taken place, the solution on the underside of the PatchPlate™ is changed to one containing amphotericin B. This permeabilises the patch of cell membrane covering the hole in each well and in effect allows a perforated, whole-cell patch clamp recording to be made.

IonWorks™ HT (a beta-test machine from Essen Instruments) was operated at room temperature (~21°C) in the following way. The reservoir in the "Buffer" position was loaded with 4 ml of PBS and that in the "Cells" position with the CHO-hERG cell suspension described above. A 96-well plate (V-bottom, Greiner Bio-one) containing the compounds to be tested (at 3X their final test concentration) was placed in the "Plate 1" position and a PatchPlate™ was clamped into the PatchPlate™ station. Each compound plate was laid-out in 12 columns to enable ten, 8-point concentration-effect curves to be constructed; the remaining two columns on the plate were taken up with vehicle (final concentration 0.33% DMSO), to define the assay baseline, and a supra-maximal blocking concentration of cisapride (final concentration 10 µM), to define the 100% inhibition level. The fluidics-head (F-Head) of IonWorks™ HT then added 3.5 µl of PBS to each well of the PatchPlate™ and its underside was perfused with "internal" solution that had the following composition (in mM): K-Gluconate 100, KCl 40, MgCl<sub>2</sub> 3.2, EGTA 3 and HEPES 5 (all Sigma) (pH 7.25-7.30 using 10 M KOH). After priming and de-bubbling, the electronics-head (E-head) then moved round the PatchPlate™ performing a hole test (i.e. applying a voltage pulse to determine whether the hole in each well was open). The F-head then dispensed 3.5 µl of the cell suspension described above into each well of the PatchPlate™ and the cells were given 200 seconds to reach and seal to the hole in each well. Following this, the E-head moved round the PatchPlate™ to determine the seal resistance obtained in each well. Next, the solution on the underside of the PatchPlate™ was changed to "access" solution that had the following composition (in mM): KCl 140, EGTA 1, MgCl<sub>2</sub> 1 and HEPES 20 (pH 7.25-7.30 using 10 M KOH) plus 100 µg/ml of amphotericin B (all Sigma). After allowing 9 minutes for patch perforation to take place, the E-head moved round the PatchPlate™ 48 wells at a time to obtain pre-compound hERG current measurements. The F-head then added 3.5 µl of solution from each well of the compound plate to 4 wells on the PatchPlate™ (the final DMSO concentration was 0.33% in every well). This was achieved by moving from the most dilute to

the most concentrated well of the compound plate to minimise the impact of any compound carry-over. After approximately three and a half minutes incubation, the E-head then moved around all 384-wells of the PatchPlate™ to obtain post-compound hERG current measurements. In this way, non-cumulative concentration-effect curves could be produced where, providing the acceptance criteria were achieved in a sufficient percentage of wells (see below), the effect of each concentration of test compound was based on recording from between 1 and 4 cells.

The pre- and post-compound hERG current was evoked by a single voltage pulse consisting of a 20 s period holding at -70 mV, a 160 ms step to -60 mV (to obtain an estimate of leak), a 100 ms step back to -70 mV, a 1 s step to +40 mV, a 2 s step to -30 mV and finally a 500 ms step to -70mV. In between the pre- and post-compound voltage pulses there was no clamping of the membrane potential. Currents were leak-subtracted based on the estimate of current evoked during the +10mV step at the start of the voltage pulse protocol. The current signal was sampled at 2.5k Hz.

Pre- and post-scan hERG current magnitude was measured automatically from the leak subtracted traces by the IonWorks™ HT software by taking a 40ms average of the current during the initial holding period at -70mV (baseline current) and subtracting this from the peak of the tail current response. The acceptance criteria for the currents evoked in each well were: pre-scan seal resistance >60 MΩ, pre-scan hERG tail current amplitude >150 pA; post-scan seal resistance >60 MΩ. The degree of inhibition of the hERG current was assessed by dividing the post-scan hERG current by the respective pre-scan hERG current for each well.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c), (d) and (e):-

Test (a):- IC<sub>50</sub> in the range, for example, 0.001 - 1 μM;

Test (b):- IC<sub>50</sub> in the range, for example, 0.001 - 5 μM;

Test (c):- IC<sub>50</sub> in the range, for example, 0.001 - 5 μM;

Test (d):- activity in the range, for example, 1-200 mg/kg/day;

Test (e):- IC<sub>50</sub> in the range, for example, 0.001 - 5  $\mu$ M;

No physiologically unacceptable toxicity was observed in Test (d) at the effective dose for quinazoline derivatives tested of the present invention. Test (f) shows a safe margin  
5 between target and hERG activity, suggesting the unlikelihood of arrhythmia caused by inhibition of the hERG channel. Accordingly no untoward toxicological effects are expected when a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

By way of example, Table A illustrates the activity of representative compounds  
10 according to the invention. Column 2 of Table A shows IC<sub>50</sub> data from Test (a) for the inhibition of EGFR tyrosine kinase protein phosphorylation; column 3 shows IC<sub>50</sub> data from Test (a) for the inhibition of erbB2 tyrosine kinase protein phosphorylation; and column 4 shows IC<sub>50</sub> data for inhibition of phosphorylation of erbB2 in a MCF7 derived cell line in Test (c) described above:

15 Table A

Example Number	IC <sub>50</sub> ( $\mu$ M) Test (a): Inhibition of EGFR tyrosine kinase protein phosphorylation	IC <sub>50</sub> ( $\mu$ M) Test (a): Inhibition of erbB2 tyrosine kinase protein phosphorylation	IC <sub>50</sub> ( $\mu$ M) Test (c): Inhibition of erbB2 tyrosine kinase protein phosphorylation
1	0.31	0.006	0.38
4	0.061	0.005	0.044

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

20 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible

powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a quinazoline derivative of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a quinazoline derivative of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.



We have found that the compounds of the present invention possess anti-proliferative properties such as anti-cancer properties that are believed to arise from their erbB, particularly EGF and more particularly erbB2 receptor tyrosine kinase inhibitory activity. Furthermore, certain of the compounds according to the present invention possess substantially better

5 potency against the erbB2 receptor tyrosine kinase, than against other tyrosine kinases enzymes, such as EGFR tyrosine kinase. Such compounds possess sufficient potency against the erbB2 receptor tyrosine kinase that they may be used in an amount sufficient to inhibit erbB2 receptor tyrosine kinase whilst demonstrating little, or significantly lower, activity against other tyrosine kinases such as EGFR. Such compounds are likely to be useful for the

10 selective inhibition of erbB2 receptor tyrosine kinase and are likely to be useful for the effective treatment of, for example erbB2 driven tumours.

Accordingly, the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by and erbB, particularly erbB2 receptor tyrosine kinases, i.e. the compounds may be used to produce an erbB,

15 particularly an erbB2, receptor tyrosine kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for the treatment of malignant cells characterised by inhibition of the erbB, particularly the erbB2, receptor tyrosine kinase. Particularly the compounds of the invention may be used to produce an anti-proliferative and/or pro-apoptotic and/or anti-invasive effect mediated alone

20 or in part by the inhibition of erbB, particularly erbB2, receptor tyrosine kinases. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours that are sensitive to inhibition of an erbB, particularly the erbB2, receptor tyrosine kinase that are involved in the signal transduction steps which drive proliferation and survival of these tumour cells. Accordingly the compounds of the present

25 invention are expected to be useful in the treatment and/or prevention of a number of hyperproliferative disorders by providing an anti-proliferative effect. These disorders include, for example psoriasis, benign prostatic hyperplasia (BPH), atherosclerosis and restenosis and, in particular, erbB, more particularly erbB2, receptor tyrosine kinase driven tumours. Such benign or malignant tumours may affect any tissue and include non-solid tumours such as

30 leukaemia, multiple myeloma or lymphoma, and also solid tumours, for example bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval tumours.

According to this aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, for use as a medicament.

Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as  
5 defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a  
10 quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as hereinbefore defined.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

15 According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect which effect is produced alone or in part by inhibiting erbB2 receptor tyrosine kinase in a warm-blooded animal such as man.

20 According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect which effect is produced alone or in part by inhibiting erbB2 receptor tyrosine kinase in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as  
25 hereinbefore defined.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, for use in the production of an anti-proliferative effect which effect is produced alone or in part by inhibiting erbB2 receptor tyrosine kinase in a warm-blooded animal such as man.

According to a further aspect of the present invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a disease or medical condition (for example a cancer as mentioned herein) mediated alone or in part by  
5 erbB, particularly erbB2, receptor tyrosine kinase.

According to a further feature of this aspect of the invention there is provided a method for treating a disease or medical condition (for example a cancer as mentioned herein) mediated alone or in part by erbB, particularly erbB2, receptor tyrosine kinase in a warm-blooded animal, such as man, in need of such treatment, which comprises administering  
10 to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, for use in the treatment of a disease or medical condition (for example a cancer as mentioned herein)  
15 mediated alone or in part by erbB, particularly erbB2, receptor tyrosine kinase.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of one or more erbB receptor  
20 tyrosine kinases, such as EGF and/or erbB2 and/or erbB4 (especially erbB2) receptor tyrosine kinase that are involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of  
25 one or more erbB receptor tyrosine kinases, such as EGF and/or erbB2 and/or erbB4 (especially erbB2) receptor tyrosine kinase, that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt  
30 thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, for use in the prevention or treatment of those tumours which are sensitive to inhibition of one or more erbB receptor tyrosine kinases, such as EGF and/or erbB2 and/or erbB4 (especially erbB2) receptor tyrosine kinase, that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing an EGF and/or erbB2 and/or erbB4 (especially erbB2) receptor tyrosine kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing an EGF and/or erbB2 and/or erbB4 (especially erbB2) receptor tyrosine kinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, for use in providing an EGF and/or erbB2 and/or erbB4 (especially erbB2) receptor tyrosine kinase inhibitory effect.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a selective erbB2 kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a selective erbB2 kinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, for use in providing a selective erbB2 kinase inhibitory effect.

By "a selective erbB2 kinase inhibitory effect" is meant that the quinazoline derivative of Formula I is more potent against erbB2 receptor tyrosine kinase than it is against other kinases. In particular some of the compounds according to the invention are more potent against erbB2 receptor kinase than it is against other tyrosine kinases such as other erbB receptor tyrosine kinases, particularly EGFR tyrosine kinase. For example a selective erbB2 kinase inhibitor according to the invention is at least 5 times, preferably at least 10 times more potent against erbB2 receptor tyrosine kinase than it is against EGFR tyrosine kinase, as determined from the relative  $IC_{50}$  values in suitable assays (for example the by comparing the  $IC_{50}$  value from the Clone 24 phospho-erbB2 cell assay (a measure of the erbB2 tyrosine kinase inhibitory activity in cells) with the  $IC_{50}$  from the KB cell assay (a measure of the EGFR tyrosine kinase inhibitory activity in cells) for a given test compound as described above).

According to a further aspect of the present invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a cancer, for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer.

According to a further feature of this aspect of the invention there is provided a method for treating a cancer, for example a cancer selected from selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, for use in the treatment of a cancer, for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, 5 gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer.

As mentioned above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease will necessarily be varied depending upon, amongst other 10 things, the host treated, the route of administration and the severity of the illness being treated.

The compounds of the invention may be administered in the form of a pro-drug, by which we mean a compound that is broken down in a warm-blooded animal, such as man, to release a compound of the invention. A pro-drug may be used to alter the physical properties 15 and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a hydroxy group in a compound of the Formula I and *in vivo* cleavable amide derivatives that may be formed at an amino group in a compound of 20 the Formula I.

Accordingly, the present invention includes those compounds of the Formula I as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the Formula I that are produced by organic 25 synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the Formula I may be a synthetically-produced compound or a metabolically-produced compound.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I is one that is based on reasonable medical judgement as being suitable for administration to the 30 human or animal body without undesirable pharmacological activities and without undue toxicity.

Various forms of pro-drug have been described, for example in the following documents :-

- a) Methods in Enzymology, Vol. 42, p. 309 to 396, edited by K. Widder, *et al.* (Academic Press, 1985);
- 5 b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);
- c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", edited by H. Bundgaard, p. 113 to 191 (1991);
- d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1 to 38 (1992); and
- 10 e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988).

The anti-proliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

- 15 (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine
- 20 arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotère and polokinas inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like
- 25 etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example

goserelin, leuporelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 $\alpha$ -reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; *J. Med. Chem.*, 2004, **47**, 6658-6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin<sup>TM</sup>] and the anti-erbB1 antibody cetuximab [Erbix, C225]); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin<sup>TM</sup>) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474;



- Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 5 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide; inhibitors of integrin  $\alpha v \beta 3$  function and angiostatin));
- (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;
- 10 (vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;
- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial 15 nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and
- (ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, 20 approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products 25 employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the Formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of the erbB receptor tyrosine protein kinases. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the

5 search for new pharmacological agents.

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

- (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;
- 10 (ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;
- (iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;
- 15 (iv) in general, the course of reactions was followed by TLC and / or analytical LC-MS, and reaction times are given for illustration only;
- (v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;
- (vi) yields are given for illustration only and are not necessarily those which can be
- 20 obtained by diligent process development; preparations were repeated if more material was required;
- (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulfoxide (DMSO-d<sub>6</sub>) as solvent unless
- 25 otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad;
- (viii) chemical symbols have their usual meanings; SI units and symbols are used;

- (ix) solvent ratios are given in volume:volume (v/v) terms; and
- (x) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for  $m/z$  are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is  $(MH)^+$  which refers to the protonated mass ion; reference to  $M^+$  is to the mass ion generated by loss of an electron; and reference to  $M-H^+$  is to the mass ion generated by loss of a proton;
- (xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulfur atom have not been resolved;
- (xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;
- (xiii) all microwave reactions were carried out in a CEM Discover™ microwave synthesizer;
- (xiv) preparative high performance liquid chromatography (HPLC) was performed on a Gilson instrument using the following conditions:
- |                  |   |
|------------------|---|
| Column:          | 21 mm x 10 cm Hichrom RPB                         |
| Solvent A:       | Water + 0.1% trifluoroacetic acid,                |
| 20 Solvent B:    | Acetonitrile + 0.1% trifluoroacetic acid          |
| Flow rate:       | 18 ml / min                                       |
| Run time:        | 15 minutes with a 10 minute gradient from 5-95% B |
| Wavelength:      | 254 nm, bandwidth 10 nm                           |
| Injection volume | 2.0-4.0 ml;                                       |
- 25 (xv) the following abbreviations have been used:

	HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-Tetramethyluronium Hexafluoro-Phosphate;
	THF	tetrahydrofuran;
	DMF	N,N-dimethylformamide;
5	DMA	N,N-dimethylacetamide;
	DCM	dichloromethane;
	DMSO	dimethylsulfoxide;
	IPA	isopropyl alcohol;
	ether	diethyl ether; and
10	TFA	trifluoroacetic acid.

### Example 1

#### **2-Oxo-2-((2R)-2-[[4-[[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]amino}quinazolin-5-yl]oxy]methyl]pyrrolidin-1-yl)ethanol**

To a stirred solution of N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]-5-[(2R)-  
15 pyrrolidin-2-ylmethoxy]quinazolin-4-amine (290 mg, 0.64 mM) and triethylamine (97 mg, 0.96 mM) in DCM (5 ml) at 0 to 4°C was added drop-wise acetoxyacetyl chloride (96 mg, 0.70 mM). The solution was allowed to warm to ambient temperature and was stirred for 30 minutes. The solution was then diluted with DCM, washed with aqueous Na<sub>2</sub>CO<sub>3</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to a gum.

20 The gum was dissolved in 7.0M NH<sub>3</sub> / MeOH (10 ml) and stirred for 18 hours. The title compound was crystallized from the reaction mixture and washed with methanol and ether to give a white solid (118 mg, 36%); NMR spectrum (400MHz, 373°K) 1.91 (m, 1H), 2.05 (m, 3H), 3.44 (m, 2H), 4.05 (m, 2H), 4.17 (m, 1H), 4.30 (dd, 1H), 4.52 (dd, 1H), 4.59 (m, 1H), 5.72 (s, 2H), 7.06 (d, 1H), 7.21 (d, 1H), 7.27 (m, 1H), 7.36 (d, 1H), 7.60 (s, 2H), 7.70 (m,

2H), 8.09 (s, 1H), 8.22 (s, 1H), 8.44 (s, 1H), 8.52 (d, 1H), 9.92 (s, 1H); Mass spectrum  $MH^+$  510.

The N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-amine used as starting material was prepared as follows:

5 DMF (0.2 ml) was added to a suspension of 5-fluoro-3,4-dihydro-3H-quinazolin-4-one (1.64 g) in thionyl chloride (10 ml) and the mixture was stirred and heated at 80°C for 6 hours. Volatile material was removed by evaporation and the residue was azeotroped with toluene (20 ml). The resulting solid was added portion-wise to a vigorously stirred mixture of saturated sodium bicarbonate (50 ml), crushed ice (50 g) and DCM (50 ml) such that the  
10 temperature was kept below 5°C. The organic phase was separated, dried and concentrated to give 4-chloro-5-fluoroquinazoline as a solid which was used without purification (1.82 g, 99%); NMR spectrum ( $CDCl_3$ ) 7.35 - 7.45 (m, 1H), 7.85 - 7.95 (m, 2H), 9.0 (s, 1H).

A stirred partial solution of 4-chloro-5-fluoroquinazoline (10.95 g, 60 mM) and 5-aminoindazole (7.98 g, 60 mM) in isopropanol (300 ml) was heated under reflux for 3 hours.  
15 On cooling to ambient temperature, the product HCl salt was filtered off and washed with isopropanol and ether. The salt was heated with water (400 ml) / ethanol (100 ml) and the partial solution was basified with aqueous ammonia. The precipitated 5-fluoro-N-1H-indazol-5-ylquinazolin-4-amine was filtered off and washed with water to give 5-fluoro-N-1H-indazol-5-ylquinazolin-4-amine (14.91 g, 89%); NMR spectrum 7.42 (dd, 1H), 7.53 (s, 2H),  
20 7.60 (d, 1H), 7.83 (m, 1H), 8.08 (d, 2H), 8.50 (s, 1H), 9.20 (d, 1H), 13.05 (s, 1H); Mass spectrum  $MH^+$  280.

To a stirred partial solution of 5-fluoro-N-1H-indazol-5-ylquinazolin-4-amine (3.35 g, 12 mM) and 2-picolyl chloride hydrochloride (2.07 g, 12.6 mM) in DMF (60 ml) was added portion-wise sodium hydride (60% dispersion in mineral oil, 1.01 g, 25.2 mM). The reaction  
25 was maintained at ambient temperature by slight cooling and then stirred for 18 hours. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride solution (5 ml) and evaporated under high vacuum. The residue was partitioned between 2.5M aqueous NaOH and DCM and the organic phase was dried over anhydrous  $Na_2SO_4$  and evaporated. It was purified by chromatography (5% methanol / ethyl acetate) and crystallized  
30 on trituration with ether to give 5-fluoro-N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine (1.8 g, 41%); NMR spectrum 5.75 (s, 2H), 6.97 (d, 1H), 7.27 (m, 1H),

7.41 (dd, 1H), 7.54-7.75 (m, 4H), 7.84 (q, 1H), 8.12 (d, 2H), 8.50 (m, 2H), 9.23 (d, 1H); Mass spectrum  $MH^+$  371.

Sodium hydride (60% dispersion in mineral oil, 100 mg, 2.5 mM) was suspended in stirred dry THF (5 ml) and (2R)-pyrrolidin-2-ylmethanol (253 mg, 2.5 mM) was added drop-  
5 wise. After stirring for 5 to 10 minutes, 5-fluoro-N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine (370 mg, 1.0 mM) was added and the mixture was heated at 130°C for 15 minutes in a microwave reactor. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride solution (1 ml) and partitioned between 2.5M aqueous NaOH and DCM. The organic phase was dried over anhydrous  $Na_2SO_4$  and evaporated to a  
10 gum, which crystallized readily on trituration with acetonitrile giving N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-amine (332 mg, 74%); NMR spectrum 1.50 (m, 1H), 1.67 (m, 2H), 1.85 (m, 1H), 2.73 (broad, 1H), 2.84 (t, 2H), 3.60 (m, 1H), 4.07 (t, 1H), 4.29 (m, 1H), 5.75 (s, 2H), 6.97 (d, 1H), 7.15 (d, 1H), 7.30 (m, 2H), 7.70 (m, 4H), 8.13 (s, 1H), 8.40 (s, 1H), 8.44 (s, 1H), 8.51 (d, 1H), 10.64 (s, 1H);  
15 Mass spectrum  $MH^+$  452.

## Example 2

**2-Oxo-2-((2R)-2-[[[4-[[1-(1,3-thiazol-4-ylmethyl)-1H-indazol-5-yl]amino]quinazolin-5-yl]oxy]methyl]pyrrolidin-1-yl)ethanol**

The procedure described in Example 1 was substantially repeated using 5-[(2R)-  
20 pyrrolidin-2-ylmethoxy]-N-[1-(1,3-thiazol-4-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine as starting material.

The deprotection was achieved with 7.0M  $NH_3$  / MeOH and DCM for 2 days. The solution was evaporated and the title compound crystallized from ethanol in 44% yield; NMR spectrum (400MHz, 373°K) 1.92 (m, 1H), 2.05 (m, 3H), 3.43 (m, 2H), 4.04 (m, 2H), 4.17 (m,  
25 1H), 4.30 (dd, 1H), 4.53 (dd, 1H), 4.60 (m, 1H), 5.78 (s, 2H), 7.21 (d, 1H), 7.35 (d, 1H), 7.45 (d, 1H), 7.61 (dd, 1H), 7.68 (m, 2H), 8.05 (s, 1H), 8.20 (d, 1H), 8.44 (s, 1H), 9.00 (s, 1H), 9.92 (s, 1H); Mass spectrum  $MH^+$  516.

The 5-[(2R)-pyrrolidin-2-ylmethoxy]-N-[1-(1,3-thiazol-4-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine used as starting material was prepared as follows:

The 5-fluoro-N-[1-(1,3-thiazol-4-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine was prepared substantially as described in Example 1 (preparation of starting materials) using 4-(chloromethyl)-1,3-thiazole hydrochloride and 5-fluoro-N-1H-indazol-5-ylquinazolin-4-amine (obtained as described in Example 1, preparation of starting materials) in 31% yield; 5 NMR spectrum 5.79 (s, 2H), 7.42 (q, 1H), 7.50 (s, 1H), 7.59 (t, 2H), 7.72 (d, 1H), 7.81 (q, 1H), 8.18 (s, 2H), 8.50 (s, 1H), 9.03 (s, 1H), 9.22 (d, 1H); Mass spectrum  $MH^+$  377.

The 5-[(2R)-pyrrolidin-2-ylmethoxy]-N-[1-(1,3-thiazol-4-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine was prepared substantially as described in Example 1 (preparation of starting materials) using 5-fluoro-N-[1-(1,3-thiazol-4-ylmethyl)-1H-indazol-5-yl]quinazolin-10 4-amine in 81% yield; NMR spectrum 1.50 (m, 1H), 1.67 (m, 2H), 1.87 (m, 1H), 2.75 (broad, 1H), 2.84 (t, 2H), 3.60 (m, 1H), 4.07 (t, 1H), 4.29 (m, 1H), 5.77 (s, 2H), 7.13 (d, 1H), 7.31 (d, 1H), 7.50 (s, 1H), 7.70 (m, 3H), 8.08 (s, 1H), 8.38 (s, 1H), 8.48 (s, 1H), 9.02 (s, 1H), 10.63 (s, 1H); Mass spectrum  $MH^+$  458.

### Example 3

15 2-((2R)-2-[[4-[[1-(3-Fluorobenzyl)-1H-indazol-5-yl]amino]quinazolin-5-yl]oxy)methyl]pyrrolidin-1-yl)-2-oxoethanol

The procedure described in Example 1 was substantially repeated using N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-amine.

After deprotection with 7.0M  $NH_3$  / MeOH, the title compound was isolated by 20 chromatography (0-10% MeOH / DCM + 1% aqueous ammonia) followed by reverse phase HPLC (aqueous acetonitrile + TFA). Product fractions were basified with aqueous ammonia, extracted with dichloromethane and crystallized on trituration with ether to give the title compound in 34% yield; NMR spectrum (400MHz, 373°K) 1.92 (m, 1H), 2.05 (m, 3H), 3.45 (m, 2H), 4.03 (m, 2H), 4.17 (m, 1H), 4.29 (dd, 1H), 4.52 (dd, 1H), 4.60 (m, 1H), 5.68 (s, 2H), 25 7.06 (m, 3H), 7.21 (d, 1H), 7.35 (q, 2H), 7.62 (m, 2H), 7.69 (t, 1H), 8.10 (s, 1H), 8.23 (d, 1H), 8.44 (d, 1H), 9.93 (s, 1H); Mass spectrum  $MH^+$  527.

The N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-amine used as starting material was prepared as follows:

The 5-fluoro-N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]quinazolin-4-amine was prepared substantially as described in Example 1 (preparation of starting materials) using 3-fluorobenzyl chloride and 5-fluoro-N-1H-indazol-5-ylquinazolin-4-amine (obtained as described in Example 1, preparation of starting materials) in 40% yield; NMR spectrum 5 (500MHz) 5.70 (s, 2H), 7.06 (m, 2H), 7.10 (m, 1H), 7.36 (m, 1H), 7.42 (dd, 1H), 7.60 (m, 2H), 7.72 (d, 1H), 7.82 (m, 1H), 8.12 (s, 1H), 8.15 (s, 1H), 8.49 (s, 1H), 9.23 (d, 1H); Mass spectrum MH<sup>+</sup> 388.

The N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]-5-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-4-amine was prepared substantially as described in Example 1 10 (preparation of starting materials) using 5-fluoro-N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]quinazolin-4-amine in 76% yield; NMR spectrum 1.51 (m, 1H), 1.68 (m, 2H), 1.88 (m, 1H), 2.75 (broad, 1H), 2.84 (t, 2H), 3.60 (m, 1H), 4.06 (t, 1H), 4.30 (dd, 1H), 5.70 (t, 2H), 7.10 (m, 4H), 7.35 (m 2H), 7.70 (m 3H), 8.14 (s, 1H), 8.41 (s, 1H), 8.49 (s, 1H), 10.64 (s, 1H); Mass spectrum MH<sup>+</sup> 469.

#### 15 Example 4

**2-Oxo-2-((2R)-2-[[[4-[[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]amino}quinazolin-5-yl]oxy]methyl]piperidin-1-yl)ethanol**

The procedure described in Example 1 was substantially repeated using 5-[(2R)-piperidin-2-ylmethoxy]-N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine.

20 After deprotection with 7.0M NH<sub>3</sub> / MeOH, the solution was evaporated and the title compound was crystallized from ethanol in 62% yield; NMR spectrum (400MHz, 373°K) 1.47 (m, 1H), 1.69 (m, 4H), 1.91 (m, 1H), 3.1 (m, 1H), 3.81 (broad, 1H), 4.02 (m, 3H), 4.49 (dd, 1H), 4.67 (dd, 1H), 4.98 (broad, 1H), 5.73 (s, 2H), 7.05 (d, 1H), 7.27 (m, 2H), 7.35 (dd, 1H), 7.58 (m, 2H), 7.70 (m, 2H), 8.08 (s, 1H), 8.16 (d, 1H), 8.42 (s, 1H), 8.52 (m, 1H), 9.74 & 25 9.81 (2s, 1H); Mass spectrum MH<sup>+</sup> 524.

The 5-[(2R)-piperidin-2-ylmethoxy]-N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine used as starting material was prepared substantially as described in Example 1 (preparation of starting materials) using 5-fluoro-N-[1-(pyridin-2-ylmethyl)-1H-indazol-5-yl]quinazolin-4-amine (obtained as described in Example 1, preparation of starting

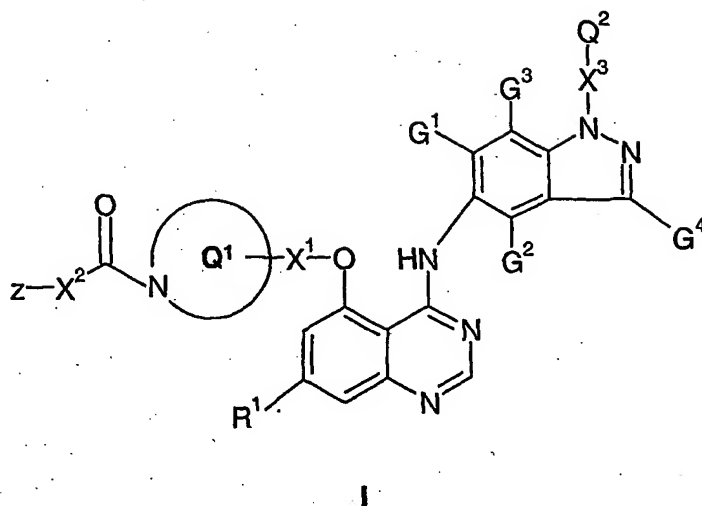


materials) and (2R)-piperidin-2-ylmethanol in 44% yield; NMR spectrum 1.22-1.82 (m, 6H), 2.41 (m, 1H), 2.61 (m, 1H), 3.03 (m, 2H), 4.15 (m, 1H), 4.27 (m, 1H), 5.75 (s, 2H), 6.95 (d, 1H), 7.10 (d, 1H), 7.30 (m, 2H), 7.70 (m, 4H), 8.12 (s, 1H), 8.43 (s, 1H), 8.49 (s, 1H), 8.52 (d, 1H), 10.74 (s, 1H); Mass spectrum  $MH^+$  466.

- 5        The (2R)-piperidin-2-ylmethanol used as starting material was prepared as follows: Trifluoroacetic acid (3 ml) was carefully added to a stirred solution of *tert*-butyl (2R)-2-(hydroxymethyl)piperidine-1-carboxylate (1.15 g, obtained as described in *Tetrahedron*, 58 (2002), 1343 - 1354) in DCM (3 ml). The reaction mixture was then stirred at room temperature for 1 hour. Volatiles were removed *in vacuo* and the oil thus obtained dissolved  
10 in methanol (60 ml), and neutralized by addition of MP-Carbonate resin (polymer supported carbonate reagent ex. Argonaut Technologies Inc.) (approximately 1g) whilst stirring at room temperature for 2 hours. The resin was filtered, washed with methanol (3 x 30 ml) and the filtrate concentrated. The resulting oil was dissolved in DCM (30 ml) and dried ( $MgSO_4$ ) before filtration and solvent removal to afford a grey oil (615 mg, 100%); NMR spectrum  
15 1.44 - 1.51 (m, 2H), 1.61 (m, 1H), 1.70 - 1.78 (m, 3H), 2.84 (m, 1H), 3.03 (m, 1H), 3.21 (d, 1H), 3.49 (m, 1H), 3.57 (dd, 1H), 5.01 (bs, 1H), 7.65 (bs, 1H); Mass spectrum  $M^+$  116.

**CLAIMS**

1. A quinazoline derivative of the Formula I:



wherein:

5  $R^1$  is selected from hydrogen, hydroxy, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkoxy;

$X^1$  is selected from a direct bond and  $C(R^2)_2$ , wherein each  $R^2$ , which may be the same or different, is selected from hydrogen and (1-4C)alkyl;

ring  $Q^1$  is a 4, 5, 6 or 7 membered saturated or partially unsaturated heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 or 2 additional heteroatoms  
 10 independently selected from oxygen, nitrogen and sulfur, and which ring is linked to the group  $X^1$  by a ring carbon atom;

$X^2$  is a group of the formula  $-(CR^3R^4)_p-$ , wherein (i)  $p$  is 1, 2, 3 or 4 and each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-4C)alkyl, or (ii)  $p$  is 1 and  $R^3$  and  $R^4$  together with the carbon atom to which they are attached represent a  
 15 cyclopropyl ring;

$Z$  is selected from hydroxy, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

$G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$ , which may be the same or different, are each selected from hydrogen and halogeno;

$X^3$  is selected from  $SO_2$ ,  $CO$ ,  $SO_2N(R^5)$  and  $C(R^5)_2$ , wherein each  $R^5$ , which may be the same or different, is selected from hydrogen and (1-4C)alkyl; and

- 5         $Q^2$  is aryl or heteroaryl, which aryl or heteroaryl group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, cyano and (1-6C)alkoxy;

and any heterocyclyl group represented by  $Q^1$  optionally bears 1 or 2 oxo or thioxo substituents;

- 10 or a pharmaceutically-acceptable salt thereof.

2.        A quinazoline derivative of the Formula I according to claim 1, wherein  $R^1$  is selected from hydrogen, hydroxy, methoxy, ethoxy and methoxyethoxy.

3.        A quinazoline derivative of the Formula I according to claim 2, wherein  $R^1$  is hydrogen.

- 15 4.        A quinazoline derivative of the Formula I according to any one or more of claims 1 to 3, wherein  $X^1$  is  $C(R^2)_2$ , wherein each  $R^2$ , which may be the same or different, is selected from hydrogen and (1-4C)alkyl.

5.        A quinazoline derivative of the Formula I according to claim 4, wherein  $X^1$  is  $CH_2$ .

6.        A quinazoline derivative of the Formula I according to any one or more of claims 1 to  
20 5, wherein the ring  $Q^1$  is a 5 or 6 membered saturated heterocyclyl group containing 1 nitrogen heteroatom and optionally 1 or 2 additional heteroatoms independently selected from oxygen, nitrogen and sulfur, and which ring is linked to the group  $X^1$  by a ring carbon atom.

7.        A quinazoline derivative of the Formula I according to claim 6, wherein the ring  $Q^1$  is  
25 selected from pyrrolidinyl and piperidinyl, and which ring is linked to the group  $X^1$  by a ring carbon atom.

8. A quinazoline derivative of the Formula I according to any one or more of claims 1 to 7, wherein  $X^2$  is a group of the formula  $-(CR^3R^4)_p-$ , wherein p is 1, 2 or 3 and each of  $R^3$  and  $R^4$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl.
9. A quinazoline derivative of the Formula I according to claim 8, wherein  $X^2$  is a group of the formula  $-(CH_2)_p-$ , wherein p is 1.
10. A quinazoline derivative of the Formula I according to any one or more of claims 1 to 9, wherein Z is selected from hydroxy, amino, methylamino, ethylamino, dimethylamino, N-methyl-N-ethylamino and di-ethylamino.
11. A quinazoline derivative of the Formula I according to claim 10, wherein Z is selected from hydroxy and dimethylamino.
12. A quinazoline derivative of the Formula I according to claim 11, wherein Z is hydroxy.
13. A quinazoline derivative of the Formula I according to any one or more of claims 1 to 12, wherein  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$ , which may be the same or different, are each selected from hydrogen, chloro and fluoro.
14. A quinazoline derivative of the Formula I according to claim 13, wherein  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  are all hydrogen.
15. A quinazoline derivative of the Formula I according to any one or more of claims 1 to 14, wherein  $X^3$  is  $C(R^5)_2$  wherein each  $R^5$ , which may be the same or different, is selected from hydrogen and (1-2C)alkyl.
16. A quinazoline derivative of the Formula I according to claim 15, wherein  $X^3$  is  $CH_2$ .
17. A quinazoline derivative of the Formula I according to any one or more of claims 1 to 16, wherein  $Q^2$  is selected from phenyl and a 5 or 6 membered monocyclic heteroaryl ring, which ring contains 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein  $Q^2$  optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, cyano and (1-6C)alkoxy.

18. A quinazoline derivative of the Formula I according to claim 17, wherein Q<sup>2</sup> is selected from phenyl, pyridyl, pyrazinyl, 1,3-thiazolyl, 1H-imidazolyl, 1H-pyrazolyl, 1,3-oxazolyl and isoxazolyl, wherein Q<sup>2</sup> optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, cyano and (1-6C)alkoxy.
19. A quinazoline derivative of the Formula I according to claim 18, wherein Q<sup>2</sup> is selected from phenyl, 2-pyridyl and 1,3-thiazol-4-yl, wherein Q<sup>2</sup> optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, cyano and (1-6C)alkoxy.
20. A quinazoline derivative of the Formula I selected from one or more of:
- 2-oxo-2-((2R)-2-[[4-[[1-(pyridin-2-yl)methyl]-1H-indazol-5-yl]amino]quinazolin-5-yl)oxy)methyl]pyrrolidin-1-yl)ethanol;
- 2-oxo-2-((2R)-2-[[4-[[1-(1,3-thiazol-4-yl)methyl]-1H-indazol-5-yl]amino]quinazolin-5-yl)oxy)methyl]pyrrolidin-1-yl)ethanol;
- 2-((2R)-2-[[4-[[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino]quinazolin-5-yl)oxy)methyl]pyrrolidin-1-yl)-2-oxoethanol; and
- 2-oxo-2-((2R)-2-[[4-[[1-(pyridin-2-yl)methyl]-1H-indazol-5-yl]amino]quinazolin-5-yl)oxy)methyl]piperidin-1-yl)ethanol;
- or a pharmaceutically-acceptable salt thereof.
21. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 20 in association with a pharmaceutically-acceptable diluent or carrier.
22. A pharmaceutical product which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 20 and an additional anti-tumour agent for the conjoint treatment of cancer.
23. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 20 for use as a medicament.

24. Use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt therefore, according to any one or more of claims 1 to 20 in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal.

25. A method for producing an anti-proliferative effect in a warm-blooded animal in need  
5 of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt therefore, according to any one or more of claims 1 to 20.

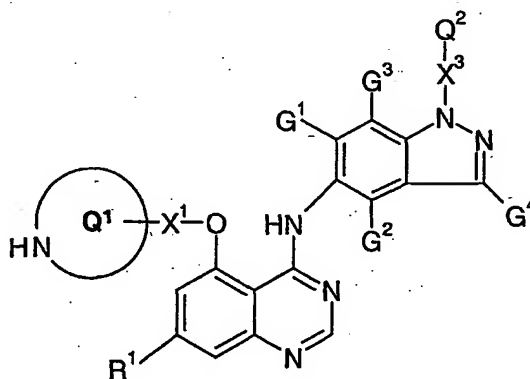
26. Use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt therefore, according to any one or more of claims 1 to 20 in the manufacture of a medicament  
10 for use in the treatment of a disease or medical condition mediated alone or in part by erbB receptor tyrosine kinase.

27. A method for treating a disease or medical condition mediated alone or in part by erbB receptor tyrosine kinase in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the  
15 Formula I, or a pharmaceutically-acceptable salt therefore, according to any one or more of claims 1 to 20.

28. Use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt therefore, according to any one or more of claims 1 to 20 in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of one  
20 or more erbB receptor tyrosine kinase that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells in a warm-blooded animal.

29. A method for the prevention or treatment of those tumours which are sensitive to inhibition of one or more erbB receptor tyrosine kinase that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells in a warm-  
25 blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt therefore, according to any one or more of claims 1 to 20.

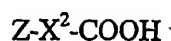
30. Use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt therefore, according to any one or more of claims 1 to 20 in the manufacture of a medicament for the treatment of cancer.
31. A method for the treatment of cancer in a warm-blooded animal in need of such  
 5 treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt therefore, according to any one or more of claims 1 to 20.
32. A process for the preparation of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt therefore, according to claim 1 which comprises:
- 10 (a) the coupling, conveniently in the presence of a suitable base, of a quinazoline of the Formula II:



II

- wherein  $R^1$ ,  $X^1$ ,  $X^3$ ,  $Q^1$ ,  $Q^2$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the meanings defined in  
 15 claim 1 except that any functional group is protected if necessary, with a carboxylic acid of the Formula III, or a reactive derivative thereof:

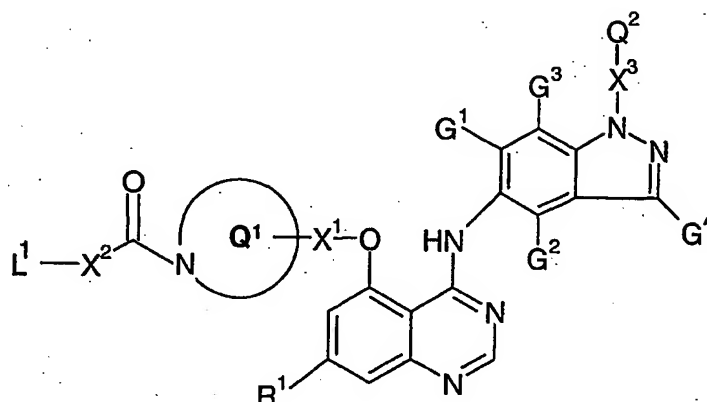
- 75 -



III

wherein Z and  $X^2$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary; or

5 (b) the coupling of a quinazoline of the Formula IV:



IV

wherein  $L^1$  is a suitable displaceable group and  $R^1$ ,  $X^1$ ,  $X^2$ ,  $X^3$ ,  $Q^1$ ,  $Q^2$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the meanings defined in claim 1 except that any functional group is protected  
 10 if necessary, with a compound of the Formula V:

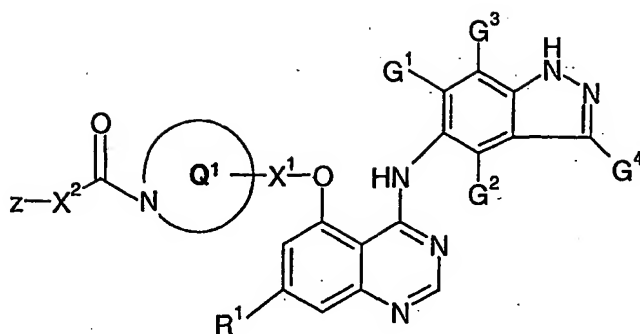


V

wherein Z has any of the meanings defined in claim 1 except that any functional group is protected if necessary; or

15 (c) the coupling, conveniently in the presence of a suitable base, of a quinazoline of the Formula VI:

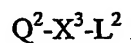




VI

wherein  $R^1$ ,  $X^1$ ,  $X^2$ ,  $Z$ ,  $Q^1$ ,  $G^1$ ,  $G^2$ ,  $G^3$  and  $G^4$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a compound of the

5 Formula VII:



VII

wherein  $L^2$  is a suitable displaceable group and  $Q^2$  and  $X^3$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary; and thereafter, if

10 necessary:

- (i) converting a quinazoline derivative of the Formula I into another quinazoline derivative of the Formula I;
- (ii) removing any protecting group that is present; and/or
- (iii) forming a pharmaceutically-acceptable salt.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/000692

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 C07D403/14 C07D417/14 A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/096226 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; HENNEQUIN, LAURENT, FRANCOIS,) 11 November 2004 (2004-11-11) cited in the application page 85 - page 112; examples 1-5, 16-21, 25, 26, 30-33 claims 1-22  ----- -/-	1-32

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*Z\* document member of the same patent family

Date of the actual completion of the international search

16 May 2006

Date of mailing of the international search report

26/05/2006

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2006/000692

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/040108 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; HENNEQUIN, LAURENT, FRANCOIS,) 15 May 2003 (2003-05-15) cited in the application page 19, line 7 - line 12 page 63; compound ID page 76, line 13 page 125; example 4.1 page 147; example 18.1 page 162; example 4.1 claims 1-24	1-32
Y	WO 03/040109 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; HENNEQUIN, LAURENT, FRANCOIS,) 15 May 2003 (2003-05-15) cited in the application page 24, line 15 page 75; compound ID page 86, line 17 - line 18 page 92, line 12 page 110, line 3 page 110, line 23 page 158; example 1.8 page 160 - page 164; examples 2.3, 4, 4.1, 4.3 claims 1-25	1-32

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2006/000692

### Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 25,27,29,31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No  
PCT/GB2006/000692

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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